AD_____

Award Number: DAMD17-97-1-7120

TITLE: New Rhenium Radiopharmaceuticals for the Selective Imaging and Therapy of Breast Cancer

PRINCIPAL INVESTIGATOR: Jeffrey B. Arterburn, Ph.D.

CONTRACTING ORGANIZATION: New Mexico State University
Las Cruces, New Mexico 88003

REPORT DATE: June 2001

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	June 2001	Final (12 May 97 - 12 May 01)

4. TITLE AND SUBTITLE
New Rhenium Radiopharmaceuticals for the Selective Imaging and Therapy of Breast Cancer

5. FUNDING NUMBERS
DAMD17-97-1-7120

6. AUTHOR(S)
Jeffrey E. Arterburn, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
New Mexico State University
Las Cruces, New Mexico 88003

E-Mail: jarterbu@nmsu.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
This report contains colored photos

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 Words)*

Several novel rhenium-estradiol complexes were synthesized as potential radiopharmaceuticals for the imaging and therapy of breast cancer. Novel palladium catalyzed carbon-carbon and carbon-nitrogen bond-forming chemistry was developed to synthesize phenyl and pyridyl hydrazine derivatives. Polymer-supported hydrazine derivatives were effective labeling substrates for synthesizing organoimidorhenium estradiol complexes. The estradiol-rhenium complexes were fully characterized structurally. The solubility and stability of the organoimidorhenium complexes in aqueous systems was investigated. Pyridylhydrazine derivatives of estradiol were found to form stable rhenium(I) carbonyl complexes, and are excellent candidates for continued investigation as diagnostic and therapeutic radiopharmaceuticals for breast cancer.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Breast Cancer	38
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

INTRODUCTION:

This final report describes work completed on award number DAMD17-97-1-7120 during the time period May 12, 1997- May 12, 2001. This project resulted in the synthesis of several novel derivatives of estradiol that form complexes with rhenium, as potential radiopharmaceuticals for the imaging and therapy of breast cancer. Novel palladium catalyzed carbon-carbon and carbon-nitrogen bond-forming chemistry was developed to synthesize a series of phenyl and pyridyl hydrazine derivatives. Polymer-supported hydrazine derivatives were found to be effective labeling substrates for the synthesis of organoimidorhenium estradiol complexes, and could be used as a kit formulation. The estradiol-rhenium complexes were fully characterized structurally, and submitted for receptor binding assays. The solubility and stability of the organoimidorhenium complexes in aqueous systems and in the presence of oxidants and amines was investigated. Pyridylhydrazine derivatives of estradiol were found to form extremely stable rhenium(I) carbonyl complexes, and are excellent candidates for continued investigation as diagnostic and therapeutic radiopharmaceuticals for breast cancer.

BODY:

The project was focused towards the accomplishment of these three technical objectives:

Technical Objective 1.
Synthesis of a series of polymer supported estradiol ligand precursors.

Technical Objective 2
Investigate and optimize the Re-imido forming reactions.

Technical Objective 3
Investigate physical characteristics and potential reactivity of Re-estradiol complexes.

A variety of estradiol precursors were synthesized from 17-α-ethynylestradiol and 17-α-ethenylestradiol by palladium-catalyzed carbon-carbon bond forming reactions with the alkyne or alkene group respectively. The Sonogashira conditions ($Pd(OAc)_2$ CuI, Et_2NH) were effective for synthesizing aryl amine and hydrazine derivatives, and a manuscript describing these results was published.[3] This paper presented the first examples of coupling an aryl halide substrate containing a free hydrazine group. The estradiol hydrazines were attached to commercially available carboxyl functionalized polymers by the formation of acyl hydrazine linkages. The Tentagel polymers were very effective, and exhibited solvent swelling in a variety of solvents. The polymer-supported acyl hydrazines were found to be effective for the synthesis of organoimidorhenium complexes. The reactivity of these polymer-supported estradiol derivatives was investigated with various rhenium complexes, and the efficiency and rates of product formation were quantified for a series composed of different organoimido precursors with varying

polymeric backbones using the stable isotope of rhenium. The optimal reaction conditions for Re-labeling were determined by monitoring the product formation using UV-Vis spectroscopy. Preparative scale reactions were performed and the product complexes were isolated in sufficient quantities for complete characterization. It was found that perrhenate (ReO_4^- the actual starting material for radiolabeling) with ^{188}Re, could be used as the starting material by including triphenylphosphine hydrochloride and tetrabutylammonium chloride in the reaction mixture. This result validated the major theme of the proposal, that a polymer-supported organoimido substrate could be used in a kit formulation to prepare Re-labeled estradiol derivatives without requiring separation of unlabeled estradiol. A manuscript describing these results was published.[2]

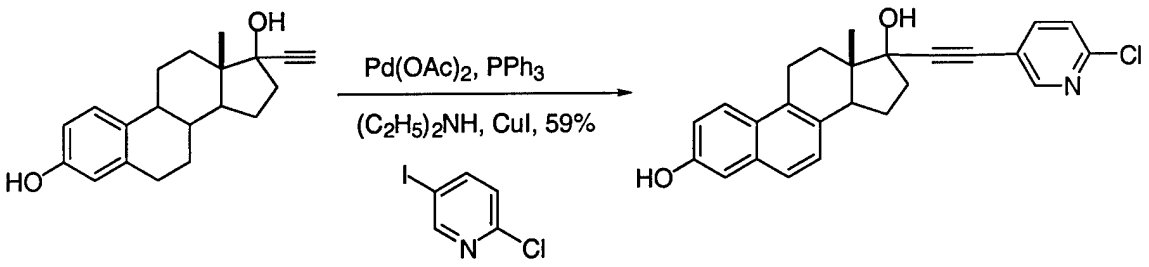
Further work involving the extrapolation of our results using the stable rhenium isotope to the ^{188}Re-radiolabeling of the polymer-supported estradiol hydrazine substrates are currently in progress in the laboratories of our collaboraters at Los Alamos National Laboratory.[7] We anticipate a continuing relationship to further develop this technology.

We have structurally characterized a variety of rhenium complexes,[2,4,5] and investigated some reactions of the imido complexes that are possible *in vivo*. The hydrolysis of the organoimido linkage to the corresponding rhenium oxo complexes was a major concern, since this would cleave the estradiol group. We found that the hydrolysis of the imido group in the bis-triphenylphosphine complexes is generally slow, requiring several hours. However, unexpectedly, we found that N-hydroxy groups dramatically accelerate the hydrolysis via an oxidative pathway involving the

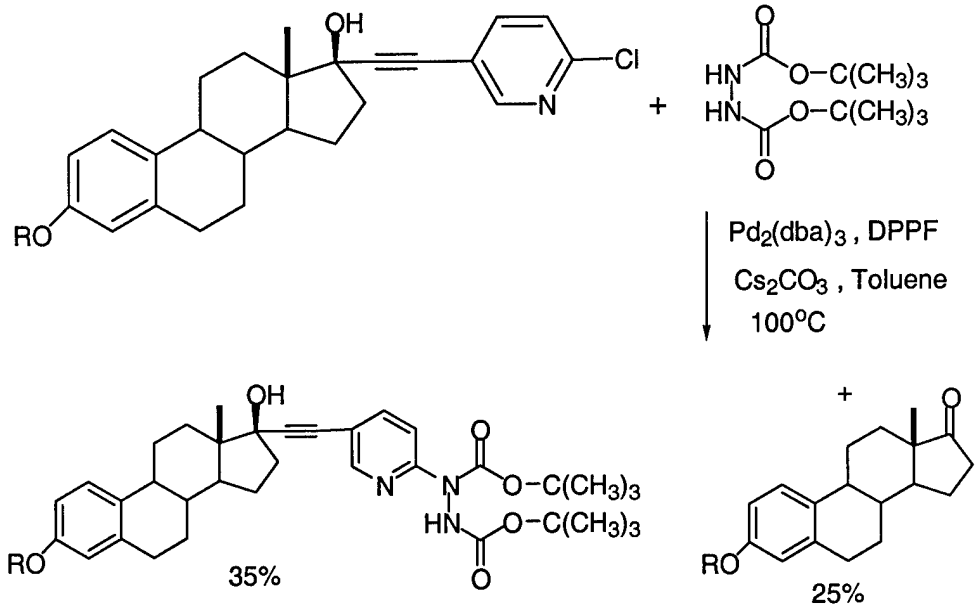
phosphine ligand followed by hydrolysis. Ligand substitution reactions were carried out to prepare dithiocarbamate complexes. These compounds were stable in the presence of mild oxidizing agents, but unfortunately underwent rapid hydrolysis in the presence of amine bases.

Recent work by Alberto and Schlibli has shown the excellent stability of rhenium(I) tricarbonyl complexes with pyridylhydrazines in water.[8] In the last year of the project we focused on synthesizing pyridyl hydrazine derivatives of estradiol that would be capable of forming stable complexes. This effort required the development of new methods for the amination of pyridyl substrates with hydrazine derivatives. ^{t}Boc-protected pyridylhydrazine derivatives were prepared from 2-pyridyl chlorides, bromides, and triflates using a one-step palladium-catalyzed amination reaction with chelating phosphine ligands. The reaction conditions were optimized and the reactivity of a series of pyridyl substrates was investigated using an Argonaut Technology's Quest 210 parallel synthesizer. Di-tert-butyl hydrazodiformate was found to be an excellent hydrazine substrate, and the resulting products were deprotected under mild conditions. This work was recently published in Organic Letters.[1]

The catalytic amination chemistry of pyridyl halides was used to synthesize estradiol derivatives. The Sonogashira coupling reaction of 2-chloro-5-iodopyridine underwent selective C-C bond formation by substitution of the iodide with ethynylestradiol to give the 2-chloropyridyl derivative. The analogous Heck coupling of vinylestradiol produced the corresponding trans-alkene in 50% yield.

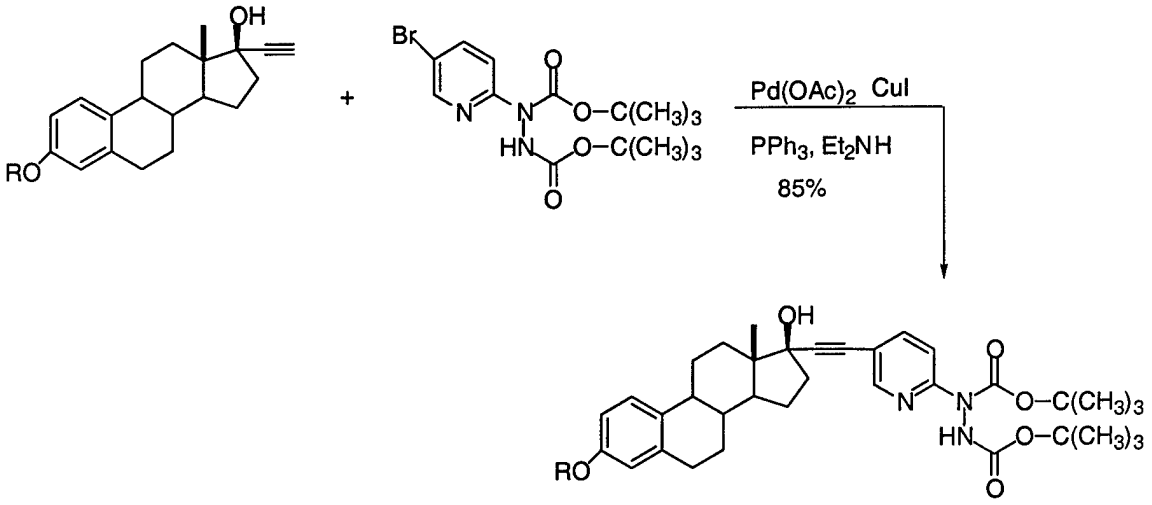


Our attempts to conduct the catalytic amination of the 2-chloropyridyl derivative were impeded by the unexpected fragmentation of the C-C bond to produce estrone as a major competing reaction. Control reactions demonstrated that palladium was essential for the degradation. The analogous alkene successfully underwent the amination in 66% yield, which indicates the unique sensitivity of the propargylic functional group under the elevated temperatures required for this reaction.

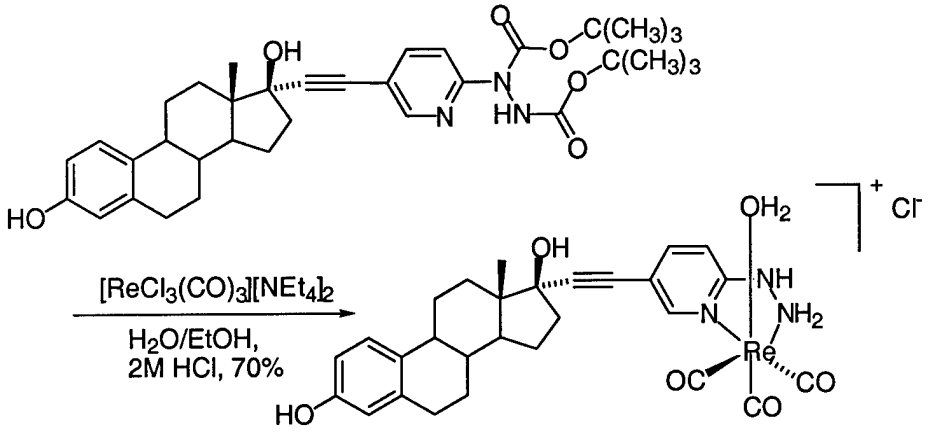


As an alternative route to the desired propargyl system we directly coupled ethynylestradiol with the 5-bromopyridyl hydrazine derivative using a Sonogashira reaction, and were delighted with the successful coupling yield of

this reaction (85%). Using vinylestradiol in an attempted Heck coupling with this substrate was unsuccessful, due to decomposition of the 5-bromopyridyl hydrazine at the elevated temperatures required for this reaction (100°C).



The estradiol pyridyl hydrazine derivatives were found to form stable complexes with the rhenium(I) tricarbonyl cation in water. The deprotection of the carbamate groups was facilitated by acidification with HCl. The complexes were stable to silica gel chromatography. A manuscript describing these results is currently in preparation. Samples will be further evaluation to determine their receptor binding affinity.



KEY RESEARCH ACCOMPLISHMENTS:

- New chemical methodology was developed, enabling for the first time the palladium catalyzed synthesis of aryl and pyridyl hydrazines.

- New technology for labeling estradiol with rhenium, compatible with instant kit type formulation, was developed.

- A variety of new rhenium-labeled estradiol derivatives were synthesized and characterized.

- The stability of organoimidorhenium linkages in aqueous systems was evaluated for the first time.

- A new class of estradiol derivatives possessing pyridyl hydrazine were synthesized, and have shown excellent stability, and indicate promise for continued evaluation as potential radiopharmaceuticals for diagnostic and therapeutic applications against breast cancer.

REPORTABLE OUTCOMES:

- Papers Published

1. Jeffrey B. Arterburn, Kalla Venkateswara Rao, Ranjit Ramdas, Benjamin R. Dible "Catalytic Amination of 2-Substituted Pyridines with Hydrazine Derivatives *Organic Letters* **2001**, *3*, 1351-1354.

2. Jeffrey B. Arterburn, Kalla Venkateswara Rao, and Marc C. Perry, *Angewandte Chemie* **2000**, *39*, 771-772. "Solid-Supported Hydrazine Substrate for Labeling Estradiol Ligands with Rhenium."

3. Jeffrey B. Arterburn, Kalla Venkateswara Rao, and Marc C. Perry, *Tetrahedron Letters* **2000**, *41*, 839-842. "Novel 17α-Ethynylestradiol Derivatives: Sonogashira Couplings Using Unprotected Phenylhydrazines."

4. Jeffrey B. Arterburn, Kalla Venkateswara Rao, Donna M. Goreham, Marcela V. Valenzuela, Mylena S. Holguin, Keith A. Hall, Kevin C. Ott, and Jeffrey C. Bryan, *Organometallics*, **2000**, *19*, 1789-1795. "Functionalized Re(V) Organoimido Complexes as Potential Radiopharmaceuticals (II). Synthesis, Structural Characterization, and Reactivity of N-Succinimidyl Ester Derivatives with Amines."

5. Jeffrey C. Bryan, Marc C. Perry, and Jeffrey B. Arterburn, *Acta Crystallogr. (C)*, **1998**, *54*, 1607-1608. "Trichlorooxo(triphenylphosphine)(triphenylphosphine oxide)rhenium(V)."

6. Jeffrey B. Arterburn, Kalla Venkateswara Rao, Ranjit Ramdas "Synthesis of 2-pyridylhydrazine derivatives of estradiol as ligands for

complexation with $Re(CO)_3(H_2O)_3^+$" Manuscript in preparation.

7. M. Fassbender , D.R. Phillips, K.C. Ott , and J.B. Arterburn "Non-carrier-added $^{186,188}Re$ labeled 17α-ethynylestradiol: a potential breast cancer therapy and imaging agent" J. Labeled Comp. Radiopharm. 2001 Manuscript in preparation.

- Degrees Awarded

1. Ph. D. Chemistry
   Marc C. Perry, Spring 2000
   Dissertation Title: "Rhenium-Catalyzed Heteroatom Transfer Reactions"
   Currently a postdoctoral associate at Texas A & M University.

2. M.S. Chemistry
   Ranjit Ramdas , Spring 2001
   Thesis Title: "The Catalytic Amination of Pyridyl Electrophiles with Protected Hydrazines; Synthesis of Pyridyl Derivatives of Estradiol" Currently employed.

3. B.S. Chemistry
   Marcela Valenzuela, Spring 2000. Currently a Ph.D. graduate student in chemistry at the University of Arizona.

4. B.S. Biochemistry, B.A. Chemistry
   Benjamin Dible, Spring 2001. Currently a Ph.D. graduate student in chemistry at the University of Utah.

5. B.S. Chemistry
Reymundo Villa, Spring 2001. Currently a Ph.D. graduate student in chemistry at the University of California, Los Angeles.

6. B.S. Chemistry
Cesear Corona, Spring 1999. Currently a Ph.D. graduate student in chemistry at New Mexico State University.

7. B.S. Chemical Engineering
Mylena Holguin, Spring 1999. Currently employed.

- Other Funds Obtained

The successful results from this project were used as part of the Preliminary Results section of a new proposal to the National Institutes of Health titled "Development of New Methods for Radiolabeling with Tc and Re." which was funded for the period 3/1/00 to 2/28/04.

- Presentations

1. "Catalytic amination of 2-pyridyl systems with hydrazine derivatives" R. Ramdas, R. V. Kalla, B. R. Dible, J. B. Arterburn 221st American Chemical Society National Meeting, San Diego, CA April 1-5, 2001.

2. "Instant Kits for Labeling Estradiol with Rhenium." Jeffrey B. Arterburn, Era of Hope, Department of Defense (DOD) Breast Cancer Research Program (BCRP) Meeting. June 8-12, 2000. Atlanta, GA.

3. "Palladium-Catalyzed Synthesis of 17-α-4-Hydrazidophenyl Estradiol Derivatives and Their Conversion to Organoimidorhenium(V) Complexes." Kalla Venkateswara Rao, Jeffrey B. Arterburn*, Marc C. Perry, Regional Meeting of the American Chemical Society, El Paso Texas, October 21-22 1999.

4. "Palladium-Catalyzed Synthesis of 17-α-4-Hydrazidophenyl Estradiol Derivatives and Their Conversion to Organoimidorhenium(V) Complexes." Kalla Venkateswara Rao, Jeffrey B. Arterburn*, Marc C. Perry, 218th National Meeting of the American Chemical Society, New Orleans, LA August 22-26 1999.

5. "Solid-Supported "Instant Kits" for Labeling Estradiol Ligands with Rhenium." Jeffrey B. Arterburn, Kalla Venkateswara Rao, Marc C. Perry. 217th National Meeting of the American Chemical Society, Anaheim, CA March 21-25 1999.

6. "Rhenium-Catalyzed Reactions for Organic Synthesis" J. B. Arterburn, M.C. Perry,

CU/Roche Colorado Symposium in Synthetic Chemistry, May 20-22, 1998.

7. "Non-carrier-added ^{186,188}Re labeled 17α-ethynylestradiol: a potential breast cancer therapy and imaging agent" M. Fassbender , D.R. Phillips, K.C. Ott , and J.B. Arterburn, 14th International Symposium on Radiopharmaceutical Chemistry, June 10-15, 2001 Interlaken, Switzerland.

CONCLUSIONS:

Novel palladium catalyzed carbon-carbon and carbon-nitrogen bond-forming chemistry was developed to enable the synthesis of a series of phenyl and pyridyl hydrazine derivatives. This methodology was used for the synthesis of several new derivatives of estradiol that form complexes with rhenium, as potential radiopharmaceuticals for the imaging and therapy of breast cancer. Polymer-supported hydrazine derivatives were found to be effective labeling substrates for the synthesis of organoimidorhenium estradiol complexes, and could be used as a kit formulation. This technology uses the starting complex perrhenate, which is the species used for ^{188}Re labeling for nuclear medicine applications. The estradiol-rhenium complexes were fully characterized structurally, and submitted for receptor binding assays. The solubility and stability of the organoimidorhenium complexes in aqueous systems and in the presence of oxidants and amines was investigated. Hydrolysis of organoimido complexes containing phosphine ligands was accelerated by mild oxidizing agents. With ancillary dithiocarbamate ligands, hydrolysis of organoimido linkage was observed in the presence of amines. Pyridylhydrazine derivatives of estradiol were found to form extremely stable rhenium(I) carbonyl complexes, which are excellent candidates

for continued investigation as potential diagnostic and therapeutic radiopharmaceuticals for breast cancer.

REFERENCES:

1. Jeffrey B. Arterburn, Kalla Venkateswara Rao, Ranjit Ramdas, Benjamin R. Dible "Catalytic Amination of 2-Substituted Pyridines with Hydrazine Derivatives *Organic Letters* **2001**, *3*, 1351-1354.

2. Jeffrey B. Arterburn, Kalla Venkateswara Rao, and Marc C. Perry, *Angewandte Chemie* **2000**, *39*, 771-772. "Solid-Supported Hydrazine Substrate for Labeling Estradiol Ligands with Rhenium."

3. Jeffrey B. Arterburn, Kalla Venkateswara Rao, and Marc C. Perry, *Tetrahedron Letters* **2000**, *41*, 839-842. "Novel 17α-Ethynylestradiol Derivatives: Sonogashira Couplings Using Unprotected Phenylhydrazines."

4. Jeffrey B. Arterburn, Kalla Venkateswara Rao, Donna M. Goreham, Marcela V. Valenzuela, Mylena S. Holguin, Keith A. Hall, Kevin C. Ott, and Jeffrey C. Bryan, *Organometallics*, **2000**, *19*, 1789-1795. "Functionalized Re(V) Organoimido Complexes as Potential Radiopharmaceuticals (II). Synthesis, Structural Characterization, and Reactivity of N-Succinimidyl Ester Derivatives with Amines."

5. Jeffrey C. Bryan, Marc C. Perry, and Jeffrey B. Arterburn, *Acta Crystallogr. (C)*, **1998**, *54*, 1607-1608. "Trichlorooxo(triphenylphosphine)-(triphenylphosphine oxide)rhenium(V)."

6. Jeffrey B. Arterburn, Kalla Venkateswara Rao, Ranjit Ramdas "Synthesis of 2-pyridylhydrazine

derivatives of estradiol as ligands for complexation with $Re(CO)_3(H_2O)_3^+$" Manuscript in preparation.

7. M. Fassbender , D.R. Phillips, K.C. Ott , and J.B. Arterburn "Non-carrier-added $^{186,188}Re$ labeled 17α-ethynylestradiol: a potential breast cancer therapy and imaging agent" J. Labeled Comp. Radiopharm. 2001, in preparation.

8. R. Alberto, R. Schibli, A. Egli, A.P. Schubiger, U. Abram, T.A. Kaden *J. Am. Chem. Soc.* **1998**, *120*, 7987-7988. "A novel organometallic aqua complex of technetium for the labeling of biomolecules: Synthesis of $[Tc\text{-}99m(OH_2)_3(CO)_3]^+$ from $[(TcO_4)\text{-}Tc\text{-}99m]^-$ in aqueous solution and its reaction with a bifunctional ligand"

APPENDICES:

Papers 1-5

Catalytic Amination of 2-Substituted Pyridines with Hydrazine Derivatives

Jeffrey B. Arterburn, Kalla Venkateswara Rao, Ranjit Ramdas, and Benjamin R. Dible

Department of Chemistry and Biochemistry, MSC 3C, New Mexico State University, P.O. Box 30001, Las Cruces, New Mexico 88003

Organic LETTERS

Reprinted from
Volume 3, Number 9, Pages 1351–1354

ORGANIC LETTERS

2001
Vol. 3, No. 9
1351−1354

Catalytic Amination of 2-Substituted Pyridines with Hydrazine Derivatives

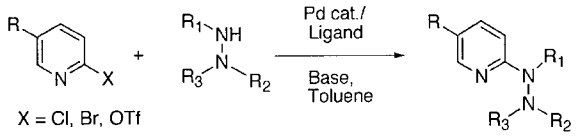
Jeffrey B. Arterburn,* Kalla Venkateswara Rao, Ranjit Ramdas, and Benjamin R. Dible

Department of Chemistry and Biochemistry, MSC 3C, New Mexico State University, P.O. Box 30001, Las Cruces, New Mexico 88003

jarterbu@nmsu.edu

Received February 20, 2001

ABSTRACT



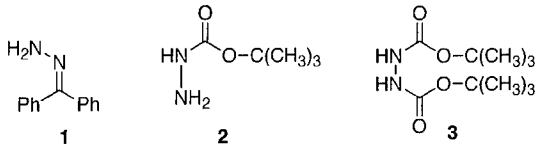
Protected pyridylhydrazine derivatives were prepared in a one-step palladium-catalyzed amination reaction using chelating phosphine ligands. 2-Pyridyl chlorides, bromides, and triflates were effective electrophiles in these reactions. Di-*tert*-butyl hydrazodiformate was an excellent hydrazine substrate, and the resulting products were deprotected under mild conditions. Catalytic amination provides a direct route to protected bifunctional hydrazinopyridine linkers that are suitable for metal-bioconjugate syntheses.

Hydrazinopyridines are important compounds for the synthesis of triazines and substituted pyridines as agrochemicals and pharmaceuticals.[1−4] 2-Pyridylhydrazines are particularly interesting synthetic targets as a result of their efficiency as ligands for a variety of metal complexes and potential applications in nuclear medicine.[5−9] Direct displacement of 2-chloropyridines with hydrazine hydrate has been used for the synthesis of 2-pyridylhydrazine derivatives, and typical reaction conditions involve heating in highly corrosive, concentrated 85% hydrazine hydrate.[10,11] These conditions also generate the powerful reducing agent diimide, which rapidly reduces alkenes and alkynes.[12] Our interest in rhenium- and technetium-labeled biomolecules as potential radiopharmaceuticals[13−15] led us to investigate metal-catalyzed amination as a possible alternative method for preparing protected 2-pyridylhydrazine derivatives that would be compatible with multistep syntheses. Catalytic amination of aryl halides and sulfonates has become an important method for preparing anilines and other arylamines.[16−23]

(1) Reich, M. F.; Fabio, P. F.; Lee, V. J.; Kuck, N. A.; Testa, R. T. *J. Med. Chem.* **1989**, *32*, 2474−2485.
(2) Di Grandi, M. J.; Tilley, J. W. *Tetrahedron Lett.* **1996**, *37*, 4327−4330.
(3) Zhang, L.-h.; Tan, Z. *Tetrahedron Lett.* **2000**, *41*, 3025−3028.
(4) Brosse, N.; Pinto, M. F.; Jamart-Gregoire, B. *J. Org. Chem.* **2000**, *63*, 4370−4374.
(5) Abrams, M. J.; Juweid, M.; TenKate, C. I.; Schwartz, D. A.; Hauser, M. M.; Gaul, F. E.; Fuccello, A. J.; Rubin, R. H.; Strauss, H. W.; Fischman, A. J. *J. Nucl. Med.* **1990**, *31*, 2022−2028.
(6) Rose, D. J.; Maresca, K. P.; Nicholson, T.; Davison, A.; Jones, A. G.; Babich, J.; Fischman, A.; Graham, W.; DeBord, J. R. D.; Zubieta, J. *Inorg. Chem.* **1998**, *37*, 2701−2716.
(7) Edwards, D. S.; Liu, S.; Harris, A. R.; Poirier, M. J.; Ewels, B. A. *Bioconjugate Chem.* **1999**, *10*, 803−807.
(8) Harris, T. D.; Sworin, M.; Williams, N.; Rajopadhye, M.; Damphousse, P. R.; Glowacka, D.; Poirier, M. J.; Yu, K. *Bioconjugate Chem.* **1999**, *10*, 808−814.
(9) Alberto, R.; Schibli, R.; Schubiger, A. P.; Abram, U.; Pietzsch, H.-J.; Johannsen, B. *J. Am. Chem. Soc.* **1999**, *121*, 6076−6077.
(10) Fargher, R. G.; Furness, R. *J. Chem. Soc.* **1915**, *107*, 688−699.
(11) Alhaider, A. A.; Abdelkader, M. A.; Lien, E. J. *J. Med. Chem.* **1985**, *28*, 1394−1398.
(12) Corey, E. J.; Mock, W. L.; Pasto, D. J. *Tetrahedron Lett.* **1961**, 347−352.
(13) Arterburn, J. B.; Fogarty, I. M.; Hall, K. A.; Ott, K. C.; Bryan, J. C. *Angew Chem., Int. Ed. Engl.* **1996**, *35*, 2877−2879.
(14) Arterburn, J. B.; Rao, K. V.; Perry, M. C. *Angew. Chem., Int. Ed.* **2000**, *39*, 771−772.
(15) Arterburn, J. B.; Rao, K. V.; Goreham, D. M.; Valenzuela, M. V.; Holguin, M. S.; Hall, K. A.; Ott, K. C.; Bryan, J. C. *Organometallics* **2000**, *19*, 1789−1795.
(16) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860.
(17) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417−1423.
(18) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818.
(19) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146.
(20) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174.
(21) Frost, C. G.; Mendonca, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615−2623.

10.1021/ol015731y CCC: $20.00
Published on Web 04/03/2001

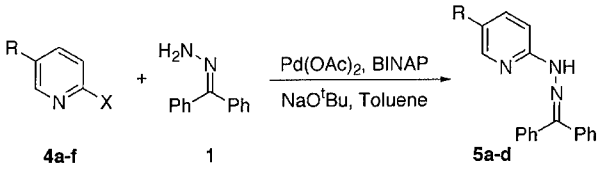
Chelating phosphine ligands enable Pd-catalyzed C−N bond formation of bromopyridines with alkyl and arylamines,[24] and sterically hindered monodentate biphenylphosphine ligands are useful for coupling chloropyridines.[20] Other examples of halopyridyl aminations catalyzed by Pd[25−31] and Ni[32−37] have been reported. There are relatively few examples of catalytic amination reactions with hydrazine derivatives. The palladium-catalyzed amination of aryl halides with benzophenone hydrazone **1** has recently been reported.[20,38−40] The protected hydrazine *tert*-butylcarbazate **2** has also been used as a substrate for Pd-catalyzed aminations.[41] Herein, we present the results of a comprehensive investigation of the catalytic amination of 2-pyridyl chlorides, bromides, and triflates with hydrazine substrates, **1**−**3**, and provide a convenient general methodology for the synthesis of protected 2-hydrazinopyridine derivatives.



1 **2** **3**

The standard conditions[38−40] for the N-arylation of **1** using 2 mol % $Pd(OAc)_2$, 2 mol % of the chelating ligand 2,2′-bis(diphenylphosphandanyl)-1,1′-binaphthyl (BINAP), and sodium *tert*-butoxide base in toluene were used for the pyridyl substrates **4a**−**f** as shown in Table 1. The hydrazone **1** was used as the limiting reagent to facilitate chromatographic purification of the products **5a**−**d**. 2-Chloropyridine **4a** was an effective substrate under these conditions. The reaction with 2-bromopyridine **4b** was faster and gave improved yields, paralleling the normal relative reactivity of aryl halides. Changing the chelating ligand from BINAP to 1,1′-bis(diphenylphosphanyl) ferrocene (DPPF) in these cases resulted in significantly lower yields. The yields were also lower when $Pd_2(dba)_3$ was used as catalyst precursor. No reaction occurred using the catalytic system $Ni(COD)_2$/DPPF/NaO^{t}Bu.[32] Selective amination of the 2-position was observed for the Pd/BINAP-catalyzed reaction of 2,5-dibromopyridine **4c** with **1** in very good yield.

Table 1. Coupling of 2-Pyridyl Systems with **1**[a]



4a-f **1** **5a-d**

entry	R	X	product[b]	time (h)	yield (%)
1	H	Cl, **4a**	**5a**	16	70
2	H	Br, **4b**	**5a**	8	95
3	Br	Br, **4c**	**5b**	6	80
4	$CO_2C_6Cl_5$	Cl, **4d**	**5c**	14	42
5	H	OTf, **4e**	**5a**	16	62
6	$CO_2C_2H_5$	OTf, **4f**	**5d**	16	72

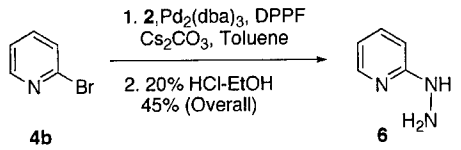
[a] All reactions were run with 2 mol % of $Pd(OAc)_2$, 2 mol % of BINAP, 0.8 equiv of **1**, 1.4 equiv of Na O^{t}Bu, and 1 equiv of pyridine derivative, at 100 °C with 2 mL of toluene for 1 mM substrate. [b] All products were characterized by ^{1}H and ^{13}C NMR and HRMS spectroscopy methods. [c] Yields of isolated product.

Activated ester derivatives of 6-hydrazidonicotinic acid are used as bifunctional labeling agents and are important synthetic compounds.[5−8] The Pd/BINAP-catalyzed amination of pentachlorophenyl ester analogue **4d** with **1** gave a moderate yield of the desired compound **5c**. We were interested in the possible catalytic amination of pyridyl triflates, since these compounds can be easily prepared from the hydroxypyridines[42] and aryl triflates have been shown to be effective substrates for Pd-catalyzed amination with anilines and alkylamines.[43−46] The direct coupling of pyridyl triflates with amines is known;[47,48] however, we observed no direct reaction between **1** and **4e** after heating a toluene solution at 100 °C for 24 h. The pyridyl triflate **4e** was converted to the hydrazone **5a** by the Pd/BINAP catalyst. The yield of **5a** from the triflate **4e** was lower than that of the halogenated substrates but comparable to the amination of aryl triflates catalyzed by $Pd(OAc)_2$/BINAP.[43] The 2-pyridyl triflates were stable under the basic reaction conditions, no competing cleavage to hydroxypyridine was

(22) Belfield, A. J.; Brown, G. R.; Foubister, A. J. *Tetrahedron* **1999**, *55*, 11399−11428.
(23) Lakshman, M. K.; Keeler, J. C.; Hilmer, J. H.; Martin, J. Q. *J. Am. Chem. Soc.* **1999**, *121*, 6090−6091.
(24) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240−7241.
(25) Ward, Y. D.; Farina, V. *Tetrahedron Lett.* **1996**, *37*, 6993−6996.
(26) Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313−1316.
(27) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620.
(28) Witulski, B. *Synlett* **1999**, *8*, 1223−1226.
(29) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hatrwig, J. F. *Org. Lett.* **2000**, *2*, 1423−1426.
(30) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403−1406.
(31) Edmondson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109−1112.
(32) Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367−6370.
(33) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054−6058.
(34) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829−12842.
(35) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 2881−2884.
(36) Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 2875−2879.
(37) Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2001**, *42*, 247−250.
(38) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2090−2093.
(39) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6621−6622.
(40) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251−10263.
(41) Wang, Z.; Skerlj, R. T.; Bridger, G. J. *Tetrahedron Lett.* **1999**, *40*, 3543−3546.
(42) Ritter, K. *Synthesis* **1993**, 735−762.
(43) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264−1267.
(44) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268−1273.
(45) Torisawa, Y.; Hashimoto, A.; Furuta, T.; Minamikawa, J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1821−1824.
(46) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101−1104.
(47) Cacchi, S.; Carangio, A.; Fabrizi, G.; Moro, L.; Pace, P. *Synlett* **1997**, 1400−1402.
(48) Schio, L.; Lemoine, G.; Klich, M. *Synlett* **1999**, 1559−1562.

observed, and excess starting material was recovered at the end of the reaction. The presence of an ethyl ester substituent in the 5-postion **4f** resulted in a mild activation and improved the yield of the hydrazone product **5d**. The proposed mechanistic model for N-arylation involves oxidative addition as the rate-determining step.[49] Coordination of pyridine has been shown to inhibit the Pd(0)/P(*o*-tolyl)$_3$-catalyzed amination of aryl bromides but does not displace bisphosphines.[24] The electron-withdrawing ester substituent decreases the ligating ability of the pyridine further to enhance the rate of oxidative addition and also is expected to facilitate the subsequent reductive elimination that produces the C−N bond.

Scheme 1. Coupling of 2-Bromopyridine **4b** with **2**



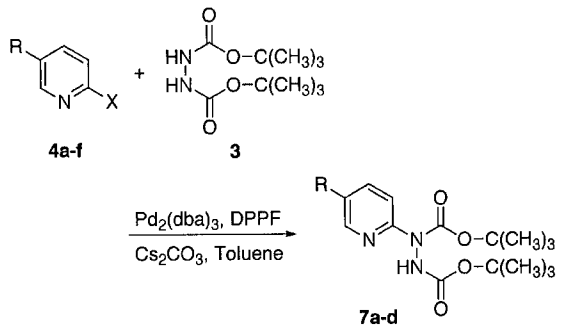
4b **6**

Electron-deficient aryl bromides and 4-nitro-2-bromopyridine have been shown to undergo Pd/DPPF amination with the protected hydrazine derivative *tert*-butylcarbazate **2**.[41] We observed that 2-bromopyridine was coupled with **2** using 8 mol % $Pd_2(dba)_3$, 12 mol % DPPF, and Cs_2CO_3 in toluene. The N-pyridyl products underwent decomposition during attempted purification by silica gel chromatography. 2-Hydrazinopyridine **6** was obtained in an overall yield of 45% from 2-bromopyridine **4b** by hydrolysis of the crude reaction mixture using 20% HCl/EtOH, followed by neutralization and extraction with ether. No reaction of **2** with 2-bromopyridine was observed using the catalytic system Pd(OAc)$_2$/BINAP/NaO^{t}Bu that was effective with the hydrazone **1**, and no reaction occurred using Ni catalysts with various chelating ligands.[32−37]

The limited success we observed for coupling pyridyl substrates with **2** led us to investigate the possibility of Pd-catalyzed amination using the symmetrical hydrazine derivative di-*tert*-butyl hydrazodiformate **3**, Table 2.

Catalytic N-arylations with protected amines such as carbamates have generally been difficult,[46,50] and no examples of catalytic C−N bond formation using **3** have been reported. Using 2 mol % $Pd_2(dba)_3$/3 mol % DPPF/Cs_2CO_3 in toluene, the reaction of 2-chloropyridine was very slow (entry 1). Increasing the catalyst to 8% decreased the reaction time and improved the yield significantly (entry 2). The more reactive 2-bromopyridine gave good yields using 2−4 mol % Pd; however, the optimum results were obtained using 8 mol % of Pd (entry 5). 2,5-Dibromopyridine **4c** underwent selective coupling at the 2-position to produce **7b** in high yield. The Pd/BINAP catalyst used for the synthesis of hydrazones **5a−d** was not successful with **3**.

Table 2. Coupling of 2-Pyridyl Systems with **3**[a]



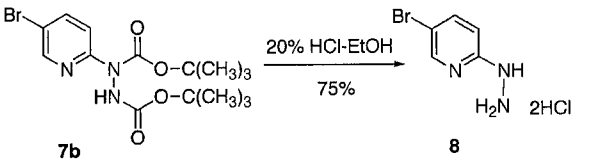
4a-f **3** **7a-d**

entry	R	X	Pd/DPPF (mol %)	time (h)	yield[b,c] (%)
1	H	Cl, **4a**	2/3	16	**7a**, 30
2	H	Cl, **4a**	8/12	16	**7a**, 70
3	H	Br, **4b**	2/3	16	**7a**, 61
4	H	Br, **4b**	4/6	8	**7a**, 61
5	H	Br,**4b**	8/12	8	**7a**, 85
6	Br	Br, **4c**	2/3	10	**7b**, 73
7	Br	Br, **4c**	8/12	6	**7b**, 85
8	$CO_2C_6Cl_5$	Cl, **4d**	8/12	14	**7c**, 45
9	H	OTf, **4e**	8/12	16	**7a**, 0
10	$CO_2C_2H_5$	OTf, **4f**	8/12	16	**7d**, 57

[a] All reactions were run with specified mol % Pd/DPPF, 0.8 equiv of **3**, 1 equiv of Cs_2CO_3, and 1 equiv of pyridine derivative at 100 °C with 2 mL of toluene for 1 mM substrate. [b] All products were characterized by ^{1}H and ^{13}C NMR and HRMS spectroscopy methods. [c] Yields of isolated product.

The pentachlorophenyl ester derivative of 2-chloropyridine **4d** was coupled with **3** by Pd/DPPF to produce **7c** in moderate yield. The unactivated pyridyl triflate **4e** did not react under these conditions. Efforts to couple this substrate using the catalyst ligand combination Pd(OAc)$_2$/(*o*-biphenyl)-PCy$_2$, which is effective for aryl triflates,[20] were also unsuccessful. The introduction of an ethyl ester improved the reactivity of the pyridyl triflate **4f**, such that **7d** was formed in moderate yield using Pd/DPPF.

Scheme 2. Hydrolysis of the ^{t}BOC-Protected Hydrazine **7b**



7b **8**

These results demonstrate that Pd-catalyzed aminations with **1** and **3** are efficient methods for the preparation of protected hydrazone and *tert*-butyl carbamate (^{t}BOC) protected hydrazine derivatives. To determine the relative ease of deprotection, we treated **5b** and **7b** with 20% HCl/EtOH. Under these conditions, the ^{t}BOC protecting groups of **7b** were completely hydrolyzed to furnish hydrazine dihydrochloride salt **8** in 75% yield. In contrast, the hydrazone **5b** was stable under these conditions.

(49) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618−4630.
(50) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580.

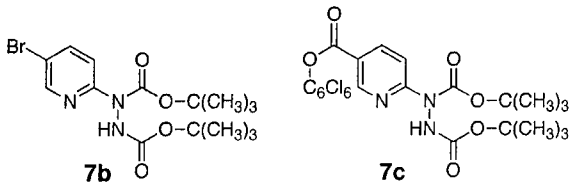


Figure 1. Protected bifunctional hydrazinopyridines.

These results illustrate the reactivity of 2-pyridyl electrophiles in Pd-catalyzed amination reactions and provide convenient methods for the synthesis of protected 2-pyridyl hydrazines. The reactions were successful using 2-pyridyl chlorides and triflates, although the best results were obtained with the bromides. The optimum reaction conditions for the pyridyl substrates with the hydrazine derivative **3** required a relatively high catalyst loading. The protected hydrazine derivative **3** was an excellent substrate for C−N bond formation and should be useful for the synthesis of a wide variety of hydrazines via catalytic amination. The hydrolysis of the 'BOC protecting groups in **7a**−**d** is considerably easier than for the hydrazone derivatives **5a**−**d**. The catalytic amination of pyridyl electrophiles with **3** provides a direct route to protected bifunctional hydrazinopyridine linkers **7b** and **7c**, which are suitable for metal-bioconjugate syntheses. Efforts to further utilize these derivatives for the synthesis of radiopharmaceuticals are currently in progress.

Acknowledgment. The authors thank the USAMRC Breast Cancer Research Program DAMD17-97-1-7120 and National Institutes of Health (GM 08136-26) for support of this work.

Supporting Information Available: Experimental procedures for **5a**−**d** and **7a**−**d** and analytical data for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

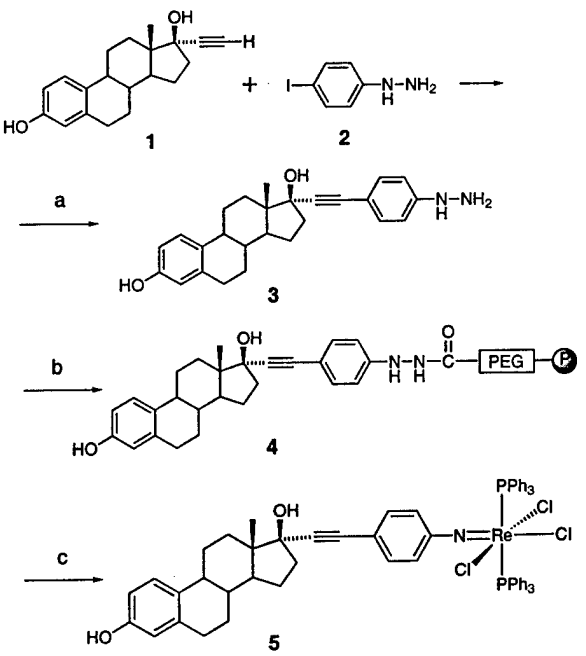
OL015731Y

Solid-Supported Hydrazine Substrate For Labeling Estradiol Ligands with Rhenium**

Jeffrey B. Arterburn,* Kalla Venkateswara Rao, and Marc C. Perry

Receptor-targeted radiopharmaceuticals offer great promise for the diagnostic imaging and therapy of tumors and other disease sites. Technetium-99m is readily available in nuclear medicine clinics throughout the world for diagnostic imaging applications, and the β-emitting radioisotopes of its congener, rhenium-186/188, are suitable for irradiating small to medium-sized tumors.[1] Radiolabeled bioligands such as steroids, peptides, and antibodies are capable of binding to receptors expressed by cancer cells, providing the selectivity needed for diagnostic and therapeutic applications.[2–4] The estrogen and progesterone steroid hormone receptors found in approximately two-thirds of breast tumors are suitable targets for steroid-based radiopharmaceuticals.[5] Radiopharmaceuticals with high specific activity are required, and the removal of all excess *unlabeled* ligand is essential to avoid competitive saturation of the binding sites of the ligand receptor. Herein we demonstrate a new strategy for labeling with rhenium using an organoimido-forming reaction of a polymer-supported hydrazine, which simultaneously establishes the steroid–radioisotope linkage and releases the labeled steroid product into solution, thereby facilitating complete removal of all unlabeled ligand by simple filtration. The approach outlined here is uniquely amenable to the specific problem of developing "instant kits" for labeling low-capacity receptor ligands, and the technology is suitable for adaptation to a wide variety of different structural classes of ligands.

The 17α position of estradiol was selected as the site for appending the linking organoimido group, following the examples of organometallic steroid derivatives which exhibit high receptor binding affinities.[6–8] We have previously synthesized highly functionalized organoimido complexes from substituted 1-acetyl 2-phenyldiazane (hydrazine derivatives) using carrier free trichlorooxobis(triphenylphosphane) rhenium(v), $[ReOCl_3(PPh_3)_2]$.[9, 10] Our approach required a convenient method for attaching pendant phenylhydrazine moieties to ethynylestradiol (**1**). The desired hydrazine **3** was obtained directly using a palladium-catalyzed coupling[11] of ethynylestradiol (**1**) with 4-iodophenyl hydrazine (**2**) in diethylamine at ambient temperature in 87% yield (Scheme 1). The free hydrazine **3** was attached to Tentagel carboxy resin (loading capacity = 0.26 mmol g^{-1}) using (1-benzotriazolyl)oxy tris(pyrrolidino) phosphonium hexafluorophosphate (PyBOP) and diisopropylethylamine in dichloromethane to give the corresponding solid-supported acetyl hydrazine derivative **4**. This reaction was monitored using FT-IR spectroscopy to follow the change in the carbonyl stretch from the free carboxylic acid (1737 cm^{-1}) to the carbohydrazide (1660 cm^{-1}), and the appearance of the characteristic aryl C–H bend at 1611 cm^{-1} from the estradiol.



Scheme 1. a) 5 mol% $Pd(OAc)_2$, 10 mol% CuI, PPh_3, $NHEt_2$, 25°C, 3 h, 87%; b) Tentagel carboxy resin, PyBOP, $NEtiPr_2$, CH_2Cl_2, 25°C, 20 h, 100% (based on loading capacity = 0.26 mmol g^{-1}); c) $[ReOCl_3(PPh_3)_2]$, PPh_3, CH_2Cl_2, 40°C, 3 h, 82%.

The organoimido-forming labeling reaction of solid-supported acetyl hydrazine **4** with $[ReOCl_3(PPh_3)_2]$ (2.86 mM in CH_2Cl_2) and triphenylphosphane occurred readily in solution to produce the air- and moisture-stable complex **5** as an olive-colored solid in 82% yield (Scheme 1). The product exhibited a single ^{31}P NMR signal due to the coordinated triphenylphosphane ligands at $\delta = -20.4$ and displayed a characteristic UV/Vis absorption spectrum with maximum at $\lambda = 370$ nm ($\varepsilon = 16200$, CH_2Cl_2).

The previous example demonstrates the efficient reactivity of the polymer-supported hydrazines. The specific requirements for radiolabeling with rhenium and technetium involve highly dilute conditions, therefore a series of labeling reactions were carried out using the polymer-supported hydrazine **4** and dilute solutions of $[ReOCl_3(PPh_3)_2]$ from 10^{-5} to 10^{-6} M (Table 1). The formation of the organoimido complex **5** was followed spectroscopically by observing the absorption maximum at $\lambda = 370$ nm. The half lives for the labeling reactions ($t_{1/2} = 2$ h) were unchanged over a 100- to 1000-fold excess of the support **4** relative to rhenium concentration. The yields of the reaction were similar when a solution of $[ReOCl_3(PPh_3)_2]$ prepared in situ from potassium perrhenate was used (entry 3, Table 1).[10] The organoimido

[*] J. B. Arterburn, K. V. Rao, M. C. Perry
Department of Chemistry and Biochemistry MSC 3C
New Mexico State University
P.O. Box 30001, Las Cruces, NM 88003 (USA)
Fax: (+1) 505-646-2649
E-mail: jarterbu@nmsu.edu

[**] This research was supported by USAMRC Breast Cancer Research Program DAMD17-97-1-7120. The authors thank Dr. R. P. Hammer and Dr. K. A. Hall for helpful discussions.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

  0570-0833/00/3904-0771 $ 17.50+.50/0

Table 1. Rhenium labeling using the solid-supported hydrazine **4**.

Entry	Concentration [10^{-5} M]	Conditions[a]	Time [h]	Yield [%]
1	2	A	2	53
			5	72
2	0.2	B	2	50
			5	70
3	9.3	C	2	54
			5	70
4	2	D	2	55
			5	65

[a] Reactions carried out in CH_2Cl_2 (10 mL) at 40 °C. Reactant ratios used: A: **4**/PPh_3/$[ReOCl_3(PPh_3)_2]$ = 100/100/1; B: **4**/PPh_3/$[ReOCl_3(PPh_3)_2]$ = 1000/1000/1; C: **4**/PPh_3/$KReO_4$ = 100/100/1; D: **4**/$HPPh_3Cl$/Bu_4NReO_4 = 100/100/1.

complex **5** was also prepared using a one-pot procedure starting with tetrabutylammonium perrhenate and triphenylphosphane hydrochloride in dichloromethane (entry 4, Table 1).

These examples illustrate a new strategy for labeling estradiol ligands with rhenium using a solid-supported hydrazine substrate, and this chemistry should also be successful for preparing technetium analogs.[12] The ability to use perrhenate and pertechnetate salts for labeling is particularly advantageous, since these species are obtained directly from the radionuclide generators. The efficiency and convenience of this approach can be extrapolated to a new generation of rhenium and technetium complexes for diagnostic and therapeutic applications in nuclear medicine. Further studies that are currently in progress involve evaluation of the receptor binding affinity and in vivo stability of these estradiol derivatives, and the extension of this technology to other low-capacity receptor systems.

Experimental Section

4: To a suspension of Tentagel Carboxy resin (1.0 g, 0.26 mmol) in dichloromethane (50 mL) was added PyBOP (405 mg, 0.78 mmol) followed by hydrazine **3** and diisopropylethylamine (0.3 mL). The resulting suspension was stirred at 25 °C for 20 h. The reaction product was filtered to give the yellow polymer support **4**. FT-IR (KBr): $\tilde{\nu}$ = 3443, 2869, 1652, 1611, 1104 cm^{-1}.

5: A suspension of **4** (110 mg, 0.0286 mmol), triphenylphosphane (7.5 mg, 0.0286 mmol), and $[ReOCl_3(PPh_3)_2]$ (23.8 mg, 0.0286 mmol) in dichloromethane (10 mL) was heated at 40 °C for 3 h. The reaction mixture was filtered, and washed thoroughly with dichloromethane. The combined organic layers were concentrated, and the product was precipitated from dichloromethane/hexanes and recrystallized to provide the complex **5** (28 mg, 82%) as olive-green crystals containing CH_2Cl_2. Elemental analysis for $C_{62}H_{57}Cl_3NO_2P_2Re \cdot 0.5\,CH_2Cl_2$: calcd: C 60.23, H 4.61, N 1.12; found: C 60.29, H 4.66, N 1.50. Spectral data is provided in the Supporting Information.

Received: September 13, 1999 [Z14014]

[1] Generator technology is available for producing $^{188}ReO_4^-$ and $^{99m}TcO_4^-$. a) S. C. Srivastava in *Current Directions in Radiopharmaceutical Research and Development* (Ed.: S. J. Mather), Kluwer Academic, Netherlands, **1996**, pp. 63–79; b) S. Mirzadeh, F. F. Knapp, Jr., *J. Radioanal. Nucl. Chem. Art.* **1996**, *203*, 471–488.

[2] W. C. Eckelman, *Eur. J. Nucl. Med.* **1995**, *22*, 249–263.

[3] R. K. Hom, J. A. Katzenellenbogen, *Nucl. Med. Biol.* **1997**, *24*, 485–498.

[4] J. R. Dilworth, S. J. Parrott, *Chem. Soc. Rev.* **1998**, *27*, 43–55.

[5] J. A. Katzenellenbogen, M. A. Welch, F. Dehdashti, *Anticancer Res.* **1997**, *17*, 1573–1576.

[6] S. Top, H. El Hafa, A. Vessières, J. Quivy, J. Vaissermann, D. W. Hughes, M. J. McGlinchey, J. P. Mornon, E. Thoreau, G. Jaouen, *J. Am. Chem. Soc.* **1995**, *117*, 8372–8380.

[7] F. Minutolo, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1998**, *120*, 13264–13265.

[8] F. Wüst, K. E. Carlson, J. A. Katzenellenbogen, H. Spies, B. Johannsen, *Steroids* **1998**, *63*, 665–671.

[9] J. B. Arterburn, I. Fogarty, K. A. Hall, K. C. Ott, J. C. Bryan, *Angew. Chem.* **1996**, *108*, 3039–3040; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2877–2879.

[10] E. C. Lisic, S. Mirzadeh, F. F. Knapp, Jr., *J. Labelled Compd. Radiopharm.* **1993**, *33*, 65–75.

[11] a) S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, *Synthesis* **1980**, 627–630; b) F. Stieber, U. Grether, H. Waldmann, *Angew. Chem.* **1999**, *111*, 1142–1145; *Angew. Chem. Int. Ed.* **1999**, *38*, 1073–1077.

[12] a) T. Nicholson, A. Davison, J. A. Zubieta, Q. Chen, A. G. Jones, *Inorg. Chim. Acta* **1995**, *230*, 205–208; b) F. D. Rochon, R. Melanson, P. C. Kong, *Inorg. Chem.* **1995**, *34*, 2273–2277.

Regioselective Lactonization of Tetrasialic Acid**

Mou-Chi Cheng, Chun-Hung Lin,* Hsiu-Yin Wang, Heng-Ru Lin, and Shih-Hsiung Wu*

Polysialic acids (PSAs) are polymers of *N*-acetylneuraminic acid. Depending on their glycosidic linkages, these sugar polymers exist in nature as α-2,8-, α-2,9-, and α-2,8/2,9-linked polysaccharides.[1] PSAs have been reported to demonstrate many important biological functions.[2] For example, α-2,8-PSA is mainly linked to the neural cell adhesion molecule (N-CAM). This homopolymer of sialic acid has been implicated in reducing N-CAM adhesion; removal of the PSA increases the adhesive capability of N-CAM.[3] In addition, α-2,8- and α-2,9-PSAs are the capsular polysaccharides of, respectively, serogroups B and C of *Neisseria meningitidis*, a leading worldwide cause of meningitis and rapidly fatal sepsis in otherwise healthy individuals.[4]

Structural diversities of PSAs are even more complicated with the possibility of PSA lactonizations. For α-2,8-PSA, the C-2 carboxylic acid of one residue can condense with the C-9 hydroxyl group of an adjacent residue to generate a δ-lactone under acidic conditions. Such δ-lactonizations have also been

[*] Prof. Dr. S.-H. Wu,[+] Prof. Dr. C.-H. Lin, M.-C. Cheng, H.-Y. Wang, H.-R. Lin
Institute of Biological Chemistry
Academia Sinica, Taipei (Taiwan)
Fax: (+886) 2-2788-3473
E-mail: shwu@gate.sinica.edu.tw, chunhung@gate.sinica.edu.tw

[+] Additional Address:
Institute of Biochemical Sciences
National Taiwan University, Taipei (Taiwan)

[**] Financial support for this work was provided by the National Science Council of Taiwan and the Academia Sinica (Taiwan).

  0570-0833/00/3904-0772 $ 17.50+.50/0

Pergamon

Tetrahedron Letters 41 (2000) 839–842

TETRAHEDRON LETTERS

Novel 17α-ethynylestradiol derivatives: Sonogashira couplings using unprotected phenylhydrazines

Jeffrey B. Arterburn,* Kalla Venkateswara Rao and Marc C. Perry

Department of Chemistry and Biochemistry MSC 3C, New Mexico State University, PO Box 30001, Las Cruces, NM 88003, USA

Received 2 November 1999; revised 23 November 1999; accepted 24 November 1999

Abstract

The Pd/Cu catalyzed coupling of 17α-ethynylestradiol with halogenated amino-substrates was investigated. Iodophenylhydrazine and its protected derivatives reacted with 17α-ethynylestradiol to give 4-hydrazinophenyl derivatives without any degradation of the hydrazine group. Unprotected 3-, and 4-iodoaniline reacted similarly to produce the aminophenyl-derivatives. Protection of the amino group of halogenated benzylamines was required for alkyne coupling reactions, in order to avoid competing *ortho*-palladation of the benzylamine substrates. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: amine; hydrazine; palladium; steroid.

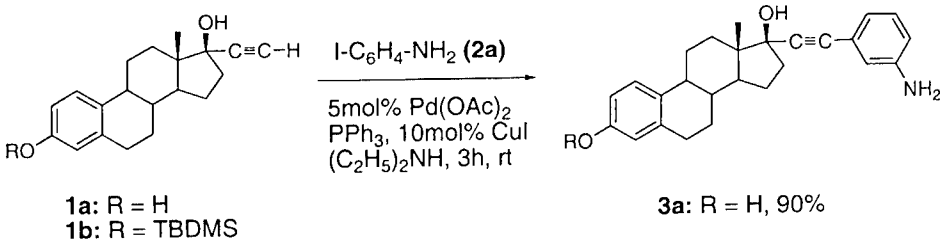
There has been a great deal of interest in the synthesis of estradiol derivatives with enhanced binding affinity for the estrogen receptor. We desired a direct route for preparing aniline, benzylamine, and phenylhydrazine derivatives appended to the ethynyl group of 17α-ethynylestradiol **1a**. The Sonogashira coupling of alkynes with aryl iodides and bromides catalyzed by Pd(O) and Cu(I) provides a mild, and efficient way to synthesize aryl alkynes;[1–5] however, very few examples of the coupling reaction with amino-substrates have been reported,[6–8] and there are no examples of the alkyne coupling reaction with halogenated unprotected phenylhydrazines. Herein we describe the synthesis of eight derivatives of 17α-ethynylestradiol, and identify the scope and limitations of the Sonogashira coupling reaction with hydrazine, and amine-containing substrates.

The Pd/Cu(I) catalyzed coupling reaction between **1a** and 3-iodoaniline **2a** in diethylamine at 25°C gave the desired *m*-aniline derivative **3a** in excellent yield (Scheme 1). The coupling was also successful using 4-iodoaniline **2b** to give the *p*-substituted compound **3b** in 89% yield (Table 1). Attempts to couple **1a** with 3-iodobenzylamine or 4-bromobenzylamine directly using these conditions were unsuccessful, and only self-coupling of the alkyne and degradation of the starting benzylic amines were observed. Benzylamines have been reported to undergo a direct *ortho*-palladation reaction with $Pd(OAc)_2$,[9,10]

* Corresponding author. Tel: (505) 646-2738; fax: (505) 646-2649; e-mail: jarterbu@nmsu.edu (J. B. Arterburn)

PII: S0040-4039(99)02205-4

which would prevent the desired catalytic cycle for alkyne coupling. The first step in the *ortho*-palladation involves coordination of the benzylamine, therefore we converted the amine to a non-coordinating derivative. The 'butoxycarbonyl-protected (BOC-) 3-iodobenzylamine **2d** reacted smoothly with **1a** to produce the coupled product **3d** in 75% yield.[7] Deprotection of this compound in 3N HCl/EtOAc gave the benzylic amine derivative **3c** in 80% yield. The coupling reaction was also successful using the BOC-protected 4-bromobenzylamine **2e**, but due to the reduced reactivity of aryl bromides, heating for 4 h at 60°C was required for complete conversion.



1a: R = H
1b: R = TBDMS

3a: R = H, 90%

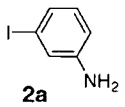
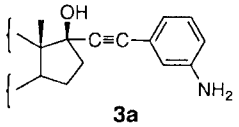
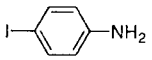
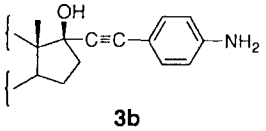
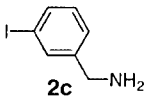
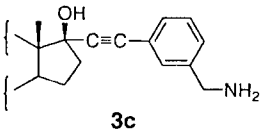
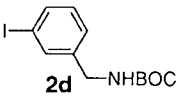
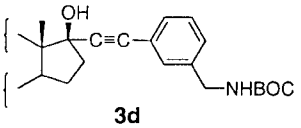
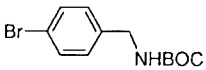
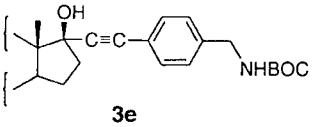
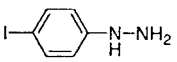
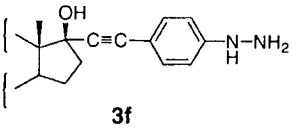
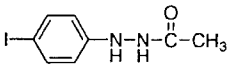
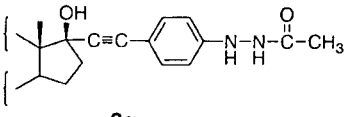
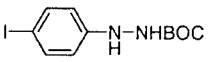
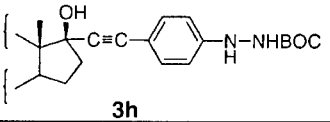
Scheme 1.

The catalytic coupling of hydrazine derivatives is complicated by the competing possibilities of hydrogen transfer chemistry, and reductive cleavage of the N–N bond.[11] The monoarylhydrazine **2f** underwent the coupling reaction catalyzed by Pd/Cu(I) to give the *p*-phenylhydrazine derivative **3f** in 87% yield. This is the first example of a coupling reaction involving an unprotected mono-substituted hydrazine. The acetyl- and BOC-protected hydrazine derivatives **2g**, and **2h** were also converted to the alkyne products in very good yields. The 'butyldimethylsilyl ether group (TBDMS) of the protected estradiol derivative **1b** and the BOC group of **2h** were stable under the mild reaction conditions which were used to produce **3h**. The hydrazine products were easily isolated by evaporation of the diethylamine solvent followed by silica gel chromatography eluted with 5% CH_3OH/CH_2Cl_2.

In summary, the Sonogashira coupling with amine and hydrazine substrates provides an efficient method for derivatizing 17α-ethynylestradiol. The mild reaction conditions, protecting group tolerance, simple workup procedures, and very good product yields are particularly advantageous. No complications from side reactions of the hydrazine group, or degradation of the sensitive phenol and tertiary alcohol functional groups of the steroid were observed. Benzylic amine substrates must first be protected before undergoing the coupling reaction, and the BOC group can be easily removed from the alkyne product. This procedure should be of general utility for the synthesis of conjugated aniline, benzylamine, and phenylhydrazine derivatives.

Typical experimental procedure: Synthesis of 17α-(3′-aminophenyl)ethynylestradiol (**3a**): A solution of palladium acetate (6.0 mg, 0.025 mmol) and triphenylphosphine (13 mg, 0.05 mmol) in diethylamine (3 mL) was stirred under argon for 10 min. Copper(I) iodide (10 mg, 0.05 mmol) and 3-iodoaniline **2a** (110 mg, 0.50 mmol) were added; after 5 min **1a** (148 mg, 0.50 mmol) was added and the reaction stirred for 3 h. Diethylamine was removed in vacuo. The residue was chromatographed on a silica gel column (25 g), eluted with 5% CH_3OH/CH_2Cl_2 to give **3a** (170 mg, 89% yield) as a white solid: mp 151–153°C; FT-IR (KBr, cm^{-1}) 3376, 1601, 1499, 786, 688; ^1H NMR (25% DMSO-d_6/$CDCl_3$) δ 8.62 (br s, 1H), 7.08 (d, J=8.8 Hz, 2H), 7.02 (t, J_1=9.0 Hz, J_2=8.2 Hz, 1H), 6.80–6.45 (m, 5H), 4.95 (br s, 1H), 2.76 (s, 2H), 2.40–1.20 (m, 14H), 0.88 (s, 3H); ^{13}C NMR δ 154.39, 146.87, 137.09, 130.41, 128.50, 125.61, 123.28, 120.06, 116.74, 114.67, 114.17, 112.35, 92.95, 84.68, 78.68, 49.05, 46.96, 43.15, 39.9, 39.5, 32.54, 29.05, 26.75, 25.99, 22.33, 12.44; anal. calcd for $C_{26}H_{29}NO_2$–$0.5H_2O$: C, 78.75; H, 7.63; N, 3.53. Found: C, 78.47; H, 7.49; N, 3.81.

Table 1
Coupling of 17α-ethynylestradiol **1a** with amines, and hydrazines[a]

Entry	Aryl halide	Coupled product	Yield (%)[b]
1	 **2a**	 **3a**	90
2	 **2b**	 **3b**	89
3	 **2c**	 **3c**	0
4	 **2d**	 **3d**	75
5	 **2e**	 **3e**	76
6	 **2f**	 **3f**	87
7	 **2g**	 **3g**	76
8	 **2h**	 **3h**	80[c]

[a] All reactions were carried out under argon at room temperature except entry 5 which was heated to 60 °C. [b] All yields are of pure products isolated by silica gel column chromatography, and all the products gave satisfactory spectral and analytical data. [c] Alkyne **1b** was used

Acknowledgements

J.B.A. thanks the USAMRC Breast Cancer Research Program DAMD17-97-1-7120 and ACS-PRF for funding. We thank the reviewer for identifying Ref. 7.

References

1. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470.
2. Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proc. Int.* **1995**, *27*, 129–160.
3. Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551–8553.
4. Top, S.; El Hafa, H.; Vessieres, A.; Quivy, J.; Vaissermann, J.; Hughes, D. W.; McGlinchey, M. J.; Mornon, J. P.; Thoreau, E.; Jaouen, G. *J. Am. Chem. Soc.* **1995**, *117*, 8372–8380.
5. Seela, F.; Zulauf, M. *Synthesis* **1996**, 726–730.
6. Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627–630.
7. Nagarajan, S. R.; Devadas, B.; Zupec, M. E.; Freeman, S. K.; Brown, D. L.; Lu, H.-F.; Mehta, P. P.; Kishore, N. S.; McWherter, C. A.; Getman, D. P.; Gordan, J. I.; Sikorski, J. A. *J. Med. Chem.* **1997**, *40*, 1422–1438.
8. Stieber, F.; Grether, U.; Waldmann, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1073–1077.
9. Fuchita, Y.; Tsuchiya, H. *Polyhedron* **1993**, *12*, 2079–2080.
10. Dunina, V. V.; Kuz'mina, L. G.; Kazakova, M. Y.; Gorunova, O. N.; Grishin, Y. K.; Kazakova, E. I. *Eur. J. Inorg. Chem.* **1999**, 1029–1039.
11. Furst, A.; Berlo, R. C.; Hooton, S. *Chem. Rev.* **1965**, *65*, 51–68.

Functionalized Rhenium(V) Organoimido Complexes as Potential Radiopharmaceuticals. 2. Synthesis, Structural Characterization, and Reactivity of *N*-Succinimidyl Ester Derivatives with Amines

Jeffrey B. Arterburn, Kalla Venkateswara Rao, Donna M. Goreham, Marcela V. Valenzuela, and Mylena S. Holguin

Department of Chemistry and Biochemistry MSC 3C, New Mexico State University, P.O. Box 30001, Las Cruces, New Mexico 88003

Keith A. Hall, Kevin C. Ott, and Jeffrey C. Bryan

CST Division, MS J514, Los Alamos National Laboratory, Los Alamos, New Mexico 87545

ORGANOMETALLICS®

Reprinted from
Volume 19, Number 9, Pages 1789–1795

Functionalized Rhenium(V) Organoimido Complexes as Potential Radiopharmaceuticals. 2. Synthesis, Structural Characterization, and Reactivity of *N*-Succinimidyl Ester Derivatives with Amines

Jeffrey B. Arterburn,* Kalla Venkateswara Rao, Donna M. Goreham,† Marcela V. Valenzuela, and Mylena S. Holguin

Department of Chemistry and Biochemistry MSC 3C, New Mexico State University, P.O. Box 30001, Las Cruces, New Mexico 88003

Keith A. Hall,‡ Kevin C. Ott, and Jeffrey C. Bryan§

CST Division, MS J514, Los Alamos National Laboratory, Los Alamos, New Mexico 87545

Received November 24, 1999

Organoimidorhenium(V) complexes were synthesized as potential labeling agents for biologically relevant organic amines using the preconjugate approach. The bistriphenylphosphine organoimidorhenium *N*-succinimidyl ester complex $Cl_3(PPh_3)_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2$ (**2**) was synthesized and characterized by single-crystal X-ray analysis. Complex **2** was coupled in aqueous dimethylformamide solvent with a series of primary and secondary amines, amino acids, and a biotin−ethylenediamine derivative to give the corresponding amide complexes in good yields. These results demonstrate that the organoimido linkage is resistant toward hydrolysis and stable in the presence of more basic alkylamines. An unusual oxygen atom transfer reaction was observed between the byproduct *N*-hydroxysuccinimide and triphenylphosphine ligands when dichloromethane was used as solvent. The dithiocarbamate complexes $Cl[Et_2NCS_2]_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2$ (**3**) and $O[(Et_2NCS_2)_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2]_2$ (**4**) were also synthesized from **2**. These complexes were unaffected by *N*-hydroxysuccinimide, but were not suitable for labeling due to hydrolysis of the organoimido groups under the reaction conditions.

Introduction

Biomolecules labeled with organometallic and coordination complexes have been developed for use as electron-transfer mediators, as probes for the active sites of enzymes, and for protein structural resolution with X-ray diffraction and electron microscopy.[1] The synthesis of radiopharmaceuticals represents another area where new technologies are necessary to overcome the challenges associated with labeling biomolecules with radioactive metals.[2] Peptides, antibodies, and steroids are all potential substrates for labeling with radioactive metals such as Tc-99m and Re-186/188 for diagnostic imaging and targeted radiotherapy, respectively. The ideal radiopharmaceutical would be easy to synthesize, exhibit stability and selective biodistribution *in vivo*, and then clear the body after the clinical procedure. These stringent requirements can ultimately be attained through multifaceted approaches leading to a diverse variety of candidate complexes for clinical trials.

Three general methods for producing metal bioconjugates are available: (1) direct labeling of biomolecules that contain a natural ligating or reactive group such as thiols; (2) the postconjugate approach where the biomolecule is first attached to a modified ligand that is then complexed with the metal; and (3) the preconjugate approach, where a metal complex is formed first and then attached to the biomolecule as an intact unit. With direct labeling it is difficult to control the site of attachment, the structure of the biomolecule can be disrupted, and redox changes at the metal can occur. The postconjugate approach provides a controlled ligand environment, but remains subject to problems during

* To whom correspondence should be addressed. E-mail: jarterbu@nmsu.edu.

† Permanent address: Glaxo Wellcome Research and Development Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, U.K.

‡ Permanent address: Symyx Technologies, Inc., 3100 Central Expressway, Santa Clara, CA 95051.

§ Permanent address: Chemical and Analytical Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831-6119.

(1) (a) Ryabov, A. D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 931−941. (b) Jaouen, G.; Vessieres, A.; Butler, I. S. *Acc. Chem. Res.* **1993**, *26*, 361−369. (c) Severin, K.; Bergs, R.; Beck, W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1634−1654.

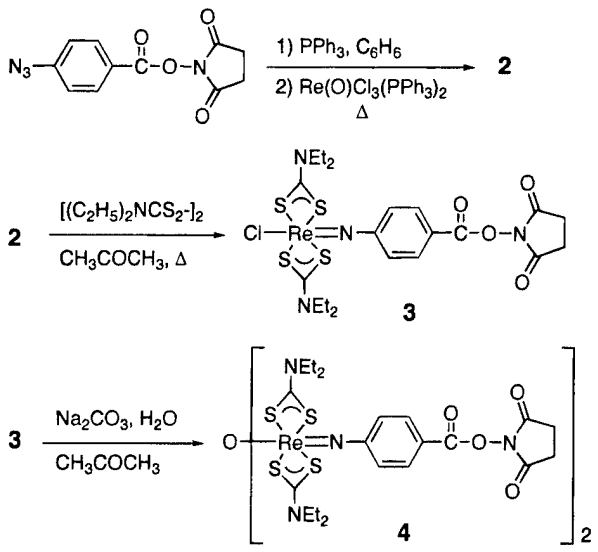
(2) (a) Jurisson, S.; Berning, D.; Jia, W.; Ma, D. *Chem. Rev.* **1993**, *93*, 1137−1156. (b) Schwochau, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2258−2267. (c) Eckelman, W. C. *Eur. J. Nucl. Med.* **1995**, *22*, 249−263. (d) Top, S.; El Hafa, H.; Vessieres, A.; Quivy, J.; Vaissermann, J.; Hughes, D. W.; McGlinchey, M. J.; Mornon, J. P.; Thoreau, E.; Jaouen, G. *J. Am. Chem. Soc.* **1995**, *117*, 8372−8380. (e) Schubiger, P. A.; Alberto, R.; Smith, A. *Bioconj. Chem.* **1996**, *7*, 165−179. (f) Fischman, A. J.; Babich, J. W. *Nucl. Med. Ann.* **1997**, 103−131. (g) Hom, R. K.; Katzenellenbogen, J. A. *Nucl. Med. Biol.* **1997**, *24*, 485−498. (h) Alberto, R.; Schibli, R.; Egli, A.; Schubiger, A. P.; Abram, U.; Kaden, T. A. *J. Am. Chem. Soc.* **1998**, *120*, 7987−7988. (i) Dilworth, J. R.; Parrott, S. J. *Chem. Soc. Rev.* **1998**, *27*, 43−55. (j) Spradau, T. W.; Katzenellenbogen, J. A. *Organometallics* **1998**, *17*, 2009−2017. (k) Waibel, R.; Alberto, R.; Willuda, J.; Finnern, R.; Schibli, R.; Stichelberger, A.; Egli, A.; Abram, U.; Mach, J. P.; Pluckthun, A.; Schubiger, P. A. *Nat. Biotechnol.* **1999**, *17*, 897−901.

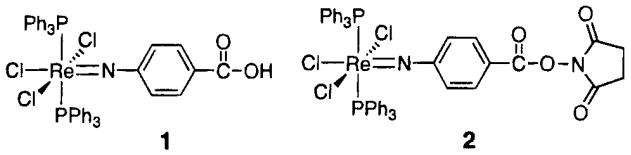
10.1021/om990929w CCC: $19.00
Publication on Web 03/31/2000

complex formation. The preconjugate approach offers greater control through the use of a purified metal complex, which only undergoes labeling with appropriately matched functional groups on the biomolecule. Amine side chain groups are commonly found on the biomolecules of interest and offer convenient sites for conjugation to a modified ligand system, due to the ease of formation of amide bonds with various activated carboxyl derivatives. Activated esters have been used to attach chelating ligands,[3] metal complexes,[4] and groups such as hydrazinopyridine to biomolecules.[5] The *N*-succinimidyl ester group is a convenient activating group for the acylation of amines and has been employed in the preconjugate approach to incorporate a variety of different classes of metal complexes,[6] including rhenium and technetium.[7]

We have investigated the suitability of the multiple bonding imido ligand for Tc and Re and recently reported the synthesis of aryl organoimido Re(V) complexes containing remotely functionalized carboxylic acid groups **1**.[8] These compounds are stable to air as solids and in solution, and Re-188 complexes can be synthesized at tracer levels and purified by HPLC chromatography using aqueous acetonitrile eluent. The multiply bonded organoimido group provides a direct covalent linkage between the organic and metal components. With this mode of attachment it is possible to fine-tune desirable properties of size, charge, and lipophilicity by varying labile ligands in the coordination sphere, an option unavailable to chelates. Therefore we have considered the development of organoimido complexes that are remotely functionalized with active ester analogues which would be suitable for labeling amines by the preconjugate approach. This approach requires that the organoimido linkage be resistant to hydrolysis under aqueous conditions and exhibit stability in the presence of alkylamines, which are both stronger bases and potential ligands. We describe here the synthesis and X-ray stucture of the activated organoimido *N*-succinimidyl ester **2** and dithiocarbamate derivatives **3** and **4**, and an investigation of their reactivity with amines, amino acids, and a biotin derivative targeted for monoclonal antibody–avidin conjugates.

Scheme 1





Results and Discussion

Synthesis and Characterization of Organoimido Succinimidyl Esters 2–4. Iminophosphoranes are known to react with rhenium(V) oxo complexes to form arylimidorhenium(V) complexes and triphenylphosphine oxide.[9] The bis-triphenylphosphine organoimidorhenium *N*-succinimidyl ester complex $Cl_3(PPh_3)_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2$ (**2**) was prepared in 91% yield by heating the rhenium(V) oxo complex $ReOCl_3(PPh_3)_2$ in benzene for 1 h with the iminophosphorane derived from *N*-succinimidyl-4-azidobenzoate (Scheme 1).[10] No precautions to dry the solvent or exclude air were required. The complex exhibits a single $^{31}P\{^1H\}$ NMR signal at δ −23.7 for the equivalent *trans* triphenylphosphine ligands. The complex was fully characterized by ^1H and ^{13}C NMR and elemental analysis. The FT-IR absorbances of the ester and imide carbonyl groups occur at 1770 and 1743 cm^{-1}, respectively. The complex exhibits a characteristic UV–vis absorbance at λ = 336 nm, ϵ = 14 030 in CH_2Cl_2 and is easily

(3) Eisenhut, M.; Lehmann, W. D.; Becker, W.; Behr, T.; Elser, H.; Strittmatter, W.; Steinstrasser, A.; Baum, R. P.; Valerius, T.; Repp, R.; Deo, Y. *J. Nucl. Med.* **1996**, *37*, 362–370.

(4) (a) Kasina, S.; Rao, T. N.; Srinivasan, A.; Sanderson, J. A.; Fitzner, J. N.; Reno, J. M.; Beaumier, P. L.; Fritzberg, A. R. *J. Nucl. Med.* **1991**, *32*, 1445–1451. (b) Linder, K. E.; Wen, M. D.; Nowotnik, D. P.; Malley, M. F.; Gougoutas, J. Z.; Nunn, A. D.; Eckelman, W. C. *Bioconjugate Chem.* **1991**, *2*, 160–170. (c) Liu, S.; Edwards, D. S.; Looby, R. J.; Poirier, M. J.; Rajopadhye, M.; Bourque, J. P.; Carroll, T. R. *Bioconjugate Chem.* **1996**, *7*, 196–202. (d) Giblin, M. F.; Jurisson, S. S.; Quinn, T. P. *Bioconjugate Chem.* **1997**, *8*, 347–353. (e) Ghulke, S.; Schaffland, A.; Zamora, P. O.; Sartor, J.; Diekman, D.; Bender, H.; Knapp, F. F.; Biersack, H. J. *Nucl. Med. Biol.* **1998**, *25*, 621–631.

(5) (a) Schwartz, D. A.; Abrams, M. J.; Hauser, M. *Bioconjugate Chem.* **1991**, *2*, 333–336. (b) Hnatowich, D. J.; Mardirossian, G.; Rusckowski, M.; Fogarasi, M.; Virzi, F.; Winnard, P. *J. Nucl. Med.* **1992**, *34*, 109–119. (c) Babich, J. W.; Solomon, H.; Pike, M. C.; Kroon, D.; Graham, W.; Abrams, M. J.; Tompkins, R. G.; Rubin, R. H.; Fischman, A. J. *J. Nucl. Med.* **1993**, *34*, 1964–1974. (d) Bridger, G. J.; Abrams, M. J.; Padmanabhan, S.; Gaul, F.; Larsen, S.; Henson, G. W.; Schwartz, D. A.; Longley, C. B.; Burton, C. A.; Ultee, M. E. *Bioconjugate Chem.* **1996**, *7*, 255–264. (e) Liu, S.; Edwards, D. S.; Barrett, J. A. *Bioconjugate Chem.* **1997**, *8*, 621–636. (f) Rose, D. J.; Maresca, K. P.; Nicholson, T.; Davison, A.; Jones, A. G.; Babich, J.; Fischman, A.; Graham, W.; DeBord, J. R. D.; Zubieta, J. *Inorg. Chem.* **1998**, *37*, 2701–2716.

(6) (a) Ryabov, A. D.; Trushkin, A. M.; Baksheeva, L. I.; Gorbatova, R. K.; Kubrakova, I. V.; Mozhaev, V. V.; Gnedenko, B. B.; Levashov, A. V. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 789–790. (b) Wang, Z.; Roe, B. A.; Nicholas, K. M.; White, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 4399–4400. (c) El Mouatassim, B.; Elamouri, H.; Vaissermann, J.; Jaouen, G. *Organometallics* **1995**, *14*, 3296–3302. (d) Gorfti, A.; Salmain, M.; Jaouen, G.; McGlinchey, M. J.; Bennouna, A.; Mousser, A. *Organometallics* **1996**, *15*, 142–151. (e) Zakrzewski, J.; Klys, A.; Bukowska-Strzyzewska, M.; Tosik, A. *Organometallics* **1998**, *17*, 5880–5886. (f) Osella, D.; Pollone, P.; Ravera, M.; Salmain, M.; Jaouen, G. *Bioconjugate Chem.* **1999**, *10*, 607–612.

(7) (a) Salmain, M.; Gunn, M.; Gorfti, A.; Top, S.; Jaouen, G. *Bioconjugate Chem.* **1993**, *4*, 425–433. (b) Salmain, M.; Gorfti, A.; Jaouen, G. *Eur. J. Biochem.* **1998**, *258*, 192–199. (c) Spradau, T. W.; Katzenellenbogen, J. A. *Bioconjugate Chem.* **1998**, *9*, 765–772. (d) Top, S.; Lehn, J. S.; Morel, P.; Jaouen, G. *J. Organomet.* **1999**, *583*, 63–68. (e) Top, S.; Morel, P.; Jaouen, G. *Inorg. Chem. Commun.* **1999**, *2*, 7–9.

(8) Arterburn, J. B.; Fogarty, I.; Hall, K. A.; Ott, K. C.; Bryan, J. C. *Angew Chem., Int. Ed. Engl.* **1996**, *35*, 2877–2879.

(9) (a) Chatt, J.; Dilworth, J. R. *J. Chem. Soc., Chem. Commun.* **1972**, 549. (b) Goeden, G. V.; Haymore, B. L. *Inorg. Chem.* **1983**, *22*, 157–167.

(10) Yip, C. C.; Yeung, C. W. T.; Moule, M. L. *Biochemistry* **1980**, *19*, 70–76.

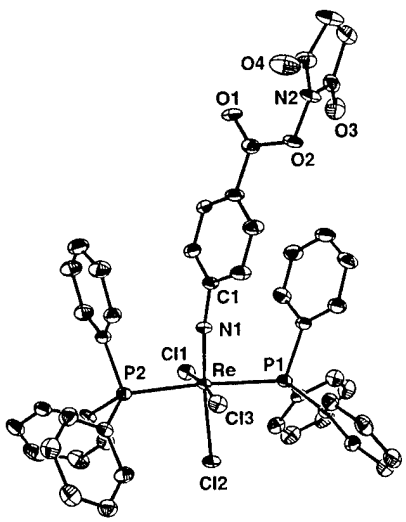


Figure 1. ORTEP drawing (50% probability ellipsoids) of $Cl_3(PPh_3)_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2{\cdot}(CH_2Cl_2)_{1.43}$-$(EtOH)_{0.57}$. Hydrogen atoms and disordered lattice molecules are omitted.

Table 1. Summary of Crystallographic Data

chemical formula	$C_{49.57}H_{44.28}Cl_{5.86}N_2O_{4.57}P_2Re$
temp (K)	203
space group	$P\bar{1}$ (No. 2)
cryst dimens (mm)	0.18 × 0.23 × 0.68
a, Å	12.703(3)
b, Å	14.250(3)
c, Å	14.930(3)
α, deg	100.04(3)
β, deg	105.40(3)
γ, deg	101.23(3)
cryst syst	triclinic
Z, volume (Å^3)	2, 1197.0
density (calcd) (g/cm^3)	1.60
abs coeff (mm^{-1})	2.88
transmission factors	0.592, 0.719
θ range for data collection (deg)	2.0–25.0
limiting indices	$-15 \le h \le 0$, $-16 \le k \le 16$, $-17 \le l \le 17$
no. of reflns collected	8965
no. of indepdt reflns, R_{int}	8537, 0.029
R^a	0.034

^{a} $R = (\Sigma||F_{obs} - F_{calc}||)/(\Sigma F_{obs})$.

Table 2. Selected Bond Lengths (Å) and Angles (deg) for 2

bond distances		bond angles	
Re–N1	1.721(4)	Re–N–C1	171.4(4)
Re–Cl1	2.440(1)	P1–Re–P2	175.3(1)
Re–Cl2	2.411(1)	Cl2–Re–Cl3	85.4(1)
Re–P1	2.524(2)	Cl1–Re–N	93.9(1)
Re–P2	2.518(2)	Cl1–Re–P1	89.7(1)
N1–C1	1.380(6)	Cl1–Re–P2	90.0(1)
O1–C7	1.211(6)	Cl1–Re–Cl2	90.4(1)

distinguished from the oxo complex $ReOCl_3(PPh_3)_2$, which absorbs at 272 nm.

The structure of the complex **2** (Figure 1) consists of an octahedral arrangement of *mer-cis*-oriented chloride ligands, *trans*-triphenylphosphine ligands, and the imido ligand. This ligand arrangement around the rhenium is similar to that of previously reported phenylimido complexes and is consistent with spectroscopic data for the complex in solution. A summary of crystallographic data is reported in Table 1. Selected bond lengths and angles are reported in Table 2. The Re–N bond length of 1.721(4) Å and the nearly linear Re–N–C1 organoimido bond angle of 171.4(4)° are typical of multiple bonded rhenium(V) monoimido complexes (1.69–1.75 Å, 156–180°).[11] The Re–Cl and Re–P distances are similar to those reported for the closely related complex $[Re(NPh)Cl_3(PPh_3)_2]$.[12] The *N*-succinimidyl ester carbonyl group of **2** is situated remotely from the coordination environment of the metal and is not perturbed by it.

The monomeric dithiocarbamate complex $Cl[Et_2NCS_2]_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2$ (**3**) was prepared in 84% yield by heating a solution of **2** with tetraethylthiuramdisulfide in acetone for 1 h (Scheme 1).[13] The ^{1}H NMR spectra of **3** in $CDCl_3$ at 22 °C shows a single triplet for the four methyl groups and a multiplet for the inequivalent CH_2 groups due to slow rotation about the C–N bond of the dithiocarbamate ligands. The ethyl groups in **3** give rise to two ^{13}C NMR peaks at δ 12.42 and 45.16. The FT-IR spectra show strong absorbances at 1531 and 997 cm^{-1} associated with the C–N and C–S bonds of the dithiocarbamate ligand. The absorbances for the ester and imide carbonyls of **3** appeared at 1769 and 1741 cm^{-1} and are very close to the corresponding carbonyl groups of complex **2**. Complex **3** exhibits a UV–vis absorbance in CH_2Cl_2 at 418 nm, ϵ = 4710 that is easily distinguished from the oxo complex $Cl[Et_2NCS_2]_2Re{=}O$, which absorbs at 344 nm.

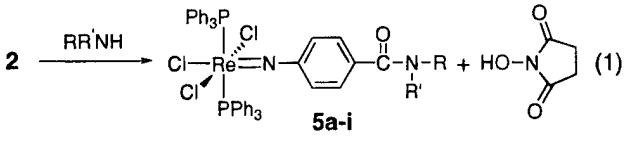
The tetrakis(dithiocarbamate) μ-oxo-dirhenium complex $O[(Et_2NCS_2)_2Re{=}N\text{-}NC_6H_4CO_2N(COCH_2)_2]_2$ (**4**) was prepared in 73% yield by treating **3** with sodium carbonate in 0.1% v/v aqueous acetone and heating for 1 h (Scheme 1).[13] The ^{1}H NMR spectra of **4** in $CDCl_3$ at 22 °C shows a single triplet for the four methyl groups and a multiplet for the CH_2 groups of the dithiocarbamate ligand. The FT-IR spectra of **4** shows strong absorbances of the dithiocarbamate ligand at 1500 and 1072 cm^{-1} and also an absorbance at 684 cm^{-1} due to the bridging μ-oxo Re–O–Re group. The absorbance of the ester carbonyl in **4** is shifted to 1780 cm^{-1}, an increase of +10 cm^{-1} compared with complexes **2** and **3**. This shift indicates the apparently greater electron-withdrawing effect of the bridging oxo group in comparison with the chloride ligand, which influences the remote conjugated carbonyl through the phenylimido group. Complex **4** showed a UV–vis absorbance at 444 nm in CH_2Cl_2; however this absorbance exhibited a nonlinear dependence on concentration. Similar deviations from the Beer–Lambert law have been observed in the electronic spectra of related oxo-bridged organoimido molybdenum dimers and were attributed to an equilibrium disproportionation reaction.[14] The corresponding oxo dimer $O[(Et_2NCS_2)_2Re{=}O]_2$ absorbs at 388 nm in CH_2Cl_2 and is easily distinguished from the organoimido complex **4**.

Stability Studies of Organoimido Succinimidyl Esters 2–4. The characteristic UV–vis absorbances of the organoimido complexes were useful for monitoring the stability of the organoimido bond toward hydrolysis in solution. For the developmental stage of this project,

(11) Wigley, D. E. *Prog. Inorg. Chem.* **1994**, *42*, 239–482.
(12) (a) Forsellini, E.; Casellato, U.; Graziani, M. C.; Carletti, M. C.; Magon, L. *Acta Crystallogr. C* **1984**, *40*, 1795–1797. (b) Wittern, U.; Strahle, J.; Abram, U. *Z. Naturforsch.* **1995**, *50b*, 997–1003.
(13) Rowbottom, J. F.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1972**, 826–830.
(14) Devore, D. D.; Maatta, E. A. *Inorg. Chem.* **1985**, *24*, 2846–2849

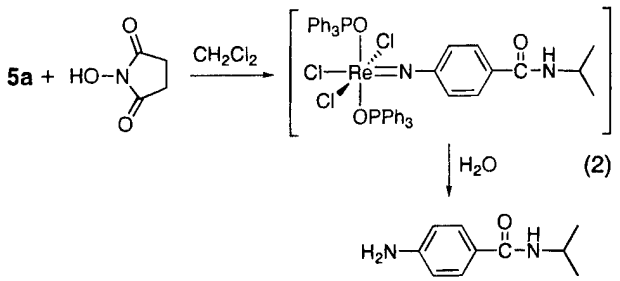
the stability of the complexes over the course of a 3 h time period was taken as representative of the necessary time for preparing, administering, and imaging a potential organoimido radiopharmaceutical. Solutions of all three of the organoimido complexes in CH_2Cl_2 or $CDCl_3$ were stable for several days at room temperature, exhibiting no change in either their absorbance spectra or their ^1H NMR. The complex **2** was not soluble in water alone, but dilute solutions (10^{-5} M) in 10% DMF/H_2O were prepared by first dissolving the complex in DMF and then diluting with H_2O. The complex **2** decomposed slowly in the aqueous media, exhibiting 30% hydrolysis after 3 h. The simple oxo complex $ReOCl_3(PPh_3)_2$ resulting from hydrolysis of the organoimido bond was observed by UV–vis, and corresponding amounts of the aniline $H_2NC_6H_4CO_2N(COCH_2)_2$ were isolated. Hydrolysis of the succinimide ester group was not observed during the 3 h time period. The monomeric chloro dithiocarbamate complex **3** rapidly dimerized in 10% DMF/H_2O to form **4**. This reaction is similar to the preparative dimerization that is carried out in aqueous acetone in the presence of base and precludes the formation of monomeric complexes from **3** in the presence of H_2O.[13] The μ-oxo dimer complex **4** was very stable in the aqueous DMF and exhibited no hydrolysis of the organoimido bond after 3 h, as evidenced by NMR and UV–vis.

Reactivity of *N*-Succinimidyl Ester 2 with Amines. The amine coupling reactions of **2** were initially conducted with isopropylamine using CH_2Cl_2 as solvent (eq 1). In this reaction the nucleophilic amine



undergoes acylation with the succinimidyl ester complex **2** to produce the amide product **5a** and 1 equiv of *N*-hydroxysuccinimide $HON(COCH_2)_2$. Because the ultimate goal was to develop practical amine labeling agents, no efforts were taken to dry solvents and reagents or to exclude air from the reactions. The amide product **5a** was isolated by precipitation with hexanes after concentrating the solvent. The complex **5a** was characterized by ^1H and ^{13}C NMR and elemental analysis. The FT-IR of **5a** shows the absorbance of the amide C=O group at 1639 cm^{-1}. The isolated yields of product **5a** from repeated experiments in CH_2Cl_2 were consistently below 30% and were accompanied by large amounts of triphenylphosphine oxide ($OPPh_3$), succinimide $HN(COCH_2)_2$, and the hydrolyzed amide $H_2NC_6H_4CONHCH(CH_3)_2$. The yields of product **5a** were not improved when this reaction was repeated using anhydrous CH_2Cl_2 under an atmosphere of argon. The isolated product **5a** was found to be stable in the presence of excess isopropylamine in CH_2Cl_2 solution for at least 6 h.

A control experiment was performed to evaluate the stability of **5a** in the presence of $HON(COCH_2)_2$, the reaction byproduct of amide formation. A 10^{-2} M solution of the amide complex **5a** in CH_2Cl_2 was treated with 2 equiv of $HON(COCH_2)_2$, and the UV–vis spectrum was monitored during the course of the reaction. The absorbance due to the coordinated PPh_3 ligands at 264 nm decreased in intensity and was completely replaced by the appearance of $OPPh_3$ after 1 h. The absorbance at 342 nm shifted slightly to 362 nm, suggesting the possible existence of a phosphine oxide complex with an intact organoimido bond. The addition of water eliminated the absorbance at 362 nm and caused decomposition of the complex along with hydrolysis of the organoimido group to produce the aniline derivative $H_2NC_6H_4CONHCH(CH_3)_2$, which was isolated from the reaction mixture in 68% yield after silica gel chromatography (eq 2). Attempts to isolate the putative phos-



phine oxide complex from these reactions and preparations carried out with exclusion of O_2 and H_2O were unsuccessful. The PPh_3 ligands in complex **5a** were not displaced by the addition of excess $OPPh_3$. The low amide coupling yields of **5a** with isopropylamine in CH_2Cl_2 can therefore be attributed to oxidation of the coordinated phosphine ligands by $HON(COCH_2)_2$, which is released after each coupling event, followed by hydrolysis of the imido bond, which occurs faster in complexes containing phosphine oxide ligands. The oxygen atom transfer chemistry to the coordinated PPh_3 from *N*-hydroxysuccinimide in CH_2Cl_2 was unexpected and to the best of our knowledge unprecedented in the literature, although various other *N*-oxides are recognized as thermodynamically favorable oxidants toward oxidation of PPh_3.[15]

The yield of the coupling reaction was significantly improved by changing the solvent to DMF, and complex **2** reacted with a series of amines to produce the corresponding amide complexes **5a–i**, Table 3. In a typical reaction, complex **2** was treated with 10 equiv of the amine in DMF (0.025 M) at 25 °C for 10 min, followed by the addition of water to precipitate the amide products. Two factors contributed to the dramatic success of this procedure: the enhanced rate of amide formation in DMF and the ability to precipitate the products with H_2O, which concentrated the $HON(COCH_2)_2$ in the aqueous phase, thereby preventing it from oxidizing bound PPh_3 ligands of the metal products. The yields of the organoimido amide products from primary and secondary amines using this procedure varied from 67% to 78%. Complexes **5a**, **5d**, **5e**, and **5f** were recrystallized from CH_2Cl_2, and the solids retained some CH_2Cl_2 solvent, which was not removed by drying in vacuo and was evident in the NMR spectra and elemental analyses of these compounds. The ethyl ester hydrochloride salts of alanine and cysteine were coupled under similar conditions in the presence of added triethylamine, producing amides **5g,h** in 67% and 74% yields, respectively. The success of the coupling reaction

(15) Holm, R. H.; Donahue, J. P. *Polyhedron* **1993**, *12*, 571–589.

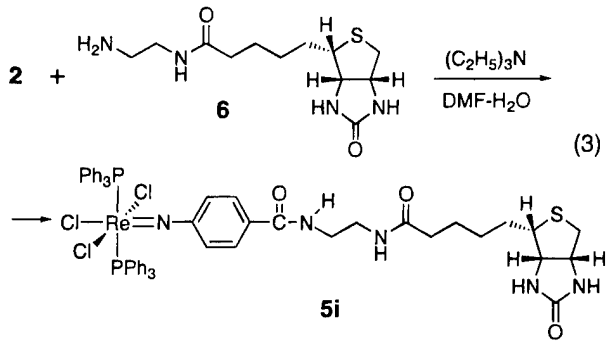
Table 3. Coupling of 1° and 2° Amines with 2[a]

entry	amine	product-amide	yield (%)
1	isopropylamine	**5a**: R′ = H R = $-CH(CH_3)_2$	70
2	2-amino-3-methylbutane	**5b**: R′ = H R = $-CH(CH_3)CH(CH_3)_2$	69
3	phenethylamine	**5c**: R′ = H R = $-CH_2CH_2-C_6H_5$	67
4	benzylamine	**5d**: R′ = H R = $-CH_2-C_6H_5$	72
5	pyrrolidine	**5e**: R = R′ = $N(CH_2CH_2)_2$	70
6	morpholine	**5f**: R′ = R = $N(CH_2CH_2)_2O$	78
7	alanine ethyl ester hydrochloride[b]	**5g**: R′ = H, R = $-CH(CH_3)CO_2CH_2CH_3$	67
8	cysteine ethyl ester hydrochloride[b]	**5h**: R′ = H, R = $CH(CH_2SH)CO_2CH_2CH_3$	74
9	**6**[b]	**5i**: R′ = H R = $-(CH_2)_2NHC(O)$biotin	49

[a] Reactions were carried out in DMF, and the product was precipitated with water. [b] Triethylamine (2 mmol) was added in the reaction mixture.

in the presence of the free sulfhydryl group of cysteine is particularly notable considering the strong potential for ligation of this group. Solutions of the cysteine complex **5h** did exhibit slow decomposition after several hours at ambient temperature, which presumably could be initiated by intermolecular ligand substitution reactions involving the sulfhydryl group.

There has been a great deal of interest in preparing labeled biotin derivatives for use in radioimmunodetection and radioimmunotherapy.[16] In the pretargeting approach, monoclonal antibody–avidin conjugates are allowed to localize at their target site, followed by treatment with a radiolabeled biotin derivitive, which is then selectively accumulated due to the high binding affinity of avidin for biotin. The ethylenediamine derivative of biotin **6** was prepared following the literature procedure.[17] The coupling reaction of **2** with **6** was performed in DMF as described above and afforded the biotin–amide derivative **5i** in 49% isolated yield (eq 3). The amide coupling proceeded to completion; however



(3)

the lower isolated yield in this case can be attributed to the solubility characteristics of the biotin moiety in **5i**, which adversely affected the precipitation of the complex. The complex was characterized by $^{31}P\{^1H\}$, ^1H, and ^{13}C NMR.

Reactivity of Dithiocarbamate Complexes 3 and 4. Recognizing the problems associated with oxidation of the phosphine ligands by *N*-hydroxysuccinimide, we decided to investigate analogous organoimido complexes containing nonoxidizable ligands. Organoimidorhenium(V) dithiocarbamate complexes are well-known and can be prepared directly from the phosphine complexes.[9b,13,18] The replacement of chloride ligands is an additional important structural difference in these types of complexes. Solutions of complexes **3** and **4** in CH_2Cl_2 and $CDCl_3$ were monitored by UV–vis and ^1H NMR, respectively, and found to be stable in the presence of excess *N*-hydroxysuccinimide for at least 3 days at ambient temperature. The dimerization of the chloro complex **3** in the presence of H_2O was described previously, and reactions of **3** with excess isopropylamine in CH_2Cl_2 containing trace amounts of water resulted in the formation of the bridging μ-oxo dimer $O[ReO(S_2CNEt_2)_2]_2$ and the hydrolyzed aniline derivative $H_2NC_6H_4CONHCH(CH_3)_2$. The dimeric succinimide ester complex **4** reacted with isopropylamine in CH_2Cl_2 with traces of H_2O to give only low yields of the desired amide product and was also accompanied by larger amounts of the hydrolysis product $O[ReO(S_2CNEt_2)_2]_2$. When the reaction of **4** with isopropylamine was performed in 10% DMF/H_2O, none of the desired bis-organoimido μ-oxo dimer $O[Re{=}N\text{-}C_6H_4CONHCH(CH_3)_2(S_2CNEt_2)_2]_2$ was isolated; only the hydrolyzed aniline and μ-oxo dimer $O[ReO(S_2CNEt_2)_2]_2$ were obtained. These results contrast with the general stability of complex **4** in aqueous DMF alone, but may simply reflect the enhanced nuleophilicity of water in the presence of an alkylamine base. Thus, while the organoimido dithiocarbamate complexes were unaffected by *N*-hydroxysuccinimide, these complexes were subject to the more severe problem of hydrolysis of the imido bond in the presence of amines.

Conclusions

A series of organoimido complexes possessing remotely functionalized succinimidyl ester groups were synthesized. The organoimidorhenium(V) *N*-hydroxysuccinimidyl ester phosphine complex **2** is an effective labeling agent for alkylamines when the reactions are carried out in aqueous DMF solution. A series of primary and secondary amines, amino acids, and a biotin–ethylenediamine derivative were successfully coupled with **2** to give the corresponding amides in good yields.

(16) (a) Koch, P.; Macke, H. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1507–1509. (b) Jeong, J. M.; Kinuya, S.; Paik, C. H.; Saga, T.; Sood, V. K.; Carrasquillo, J. A.; Neumann, R. D.; Reynolds, J. C. *Nucl. Med. Biol.* **1994**, *21*, 935–940. (c) Goodwin, D. A.; Meares, C. F.; Osen, M. *J. Nucl. Med.* **1998**, *39*, 1813–1818.

(17) Garlick, R. K.; Giese, R. W. *J. Biol. Chem.* **1988**, *263*, 210–215.

(18) Soe, K. N.; Ichimura, A.; Kitagawa, T. *Inorg. Chim. Acta* **1993**, *207*, 21–25.

These results demonstrate the stability of the organoimido linkage against competing hydrolysis to the oxo and in the presence of more basic alkylamines. When CH_2Cl_2 solvent was used, the amide formation was slower, and oxidation of the PPh_3 ligands by the released *N*-hydroxysuccinimide caused decompostion of the organoimido complexes. The dithiocarbamate complexes **3** and **4** were unaffected by *N*-hydroxysuccinimide, but the organoimido groups were not stable under the reaction conditions with alkylamines and hydrolysis to the oxo complexes was observed. The problem of PPh_3 oxidation of **2** could potentially be avoided by preparing other activated carboxylic acid derivatives such as the pentachlorophenol or nitrophenol esters. The stability of the organoimido bond is dramatically affected by the nature of the ancillary ligands, and further efforts will attempt to develop systems with enhanced stability and water solubility.

Experimental Section

General Procedures. Reagents were purchased from Aldrich or Acros and used as received. Trichlorooxobis(triphenylphosphine)rhenium(V) was prepared according to the literature procedure.[19] ^1H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, using $CDCl_3$ as solvent and internally referenced to TMS. $^{31}P\{^1H\}$ NMR spectra were obtained at 161.9 MHz, referenced to an internal capillary containing 85% $H_3PO_{4(aq)}$ ($\delta = 0$). IR spectra were recorded as KBr pellets using a Perkin-Elmer 1720 X FT-IR spectrometer. UV–vis spectra were recorded using a Hewlett-Packard 8452A diode array spectrophotometer. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

Synthesis of $Cl_3(PPh_3)_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2$ (2). Triphenylphosphine (1.57 g, 6 mmol) was added to a solution of $N_3C_6H_4CO_2N(COCH_2)_2$ (780 mg, 3.0 mmol) in benzene (200 mL) and stirred for 20 min at 25 °C, and trichlorooxobis(triphenylphosphine)rhenium(V) (2.50 g, 3.0 mmol) was then added and the mixture heated to reflux for 1 h. The volatiles were removed in vacuo, and the product was recrystallized from dichloromethane by the addition of hexanes, filtered, and washed with Et_2O and hexanes to give a green solid, **2** (2.865 g, 91% yield): UV–vis (CH_2Cl_2) $\lambda = 234, 266, 298$ ($\epsilon = 16\,400$), 336 nm ($\epsilon = 14\,030$); FT-IR 1770, 1743, 1197, 745, 694, 521 cm^{-1}; ^1H NMR δ 7.88–7.72 (m, 12H), 7.52 (d, $J = 8.6$ Hz, 2H), 7.35–7.20 (m, 18H), 6.88 (d, $J = 8.6$ Hz, 2H), 2.91 (s, 4H); ^{13}C NMR δ 169.36, 160.49, 135.21, 132.22, 131.73, 131.17, 130.78, 128.22, 123.20, 121.31, 26.07; $^{31}P\{^1H\}$ NMR δ −23.66 (s). Anal. Calcd for $C_{47}H_{38}Cl_3N_2O_4P_2Re$: C, 53.80; H, 3.65; N, 2.67. Found: C, 53.73; H, 3.65 N, 2.66.

Synthesis of $Cl[(Et)_2NCS_2]_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2$ (3). A mixture of **2** (300 mg, 0.28 mmol) and tetraethylthiuramdisulfide (170 mg, 0.57 mmol) was heated at reflux in dry acetone (20 mL) under argon for 1 h, during which time the solution became dark green. The volume was reduced to 5 mL, and the flask was cooled in an ice bath to crystallize the complex. The complex was filtered and washed with cold acetone and Et_2O to give **3** (150 mg, 84% yield): UV–vis (CH_2Cl_2): $\lambda = 234, 272, 296$ ($\epsilon = 24\,045$), 418 nm ($\epsilon = 4710$); FT-IR 1769, 1741, 1531, 1073, 997 cm^{-1}; ^1H NMR δ 7.99 (d, $J = 8.6$ Hz, 2H), 7.54 (d, $J = 8.6$ Hz, 2H) 3.95–3.65 (m, 8H), 2.89 (s, 4H), 1.38 (t, $J = 7.1$ Hz, 12H); ^{13}C NMR δ 239.88, 168.95, 161.12, 131.51, 123.81, 122.79, 45.16, 25.50, 12.42. Anal. Calcd for $C_{21}H_{28}ClN_4O_4S_4Re$: C, 33.61; H, 3.76; N, 7.47. Found: C, 33.37; H, 3.74; N, 7.41.

Synthesis of $O[((Et)_2NCS_2-)_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2]_2$ (4). To a solution of complex **3** (100 mg, 0.13 mmol) in 0.1% v/v aqueous acetone (20 mL) was added sodium carbonate (400 mg), and the mixture was heated at reflux for 2 h. The reaction mixture was filtered and concentrated in vacuo, and the crude product was isolated by addition of hexanes to a dichloromethane solution and purified by recrystallization from hexanes/CH_2Cl_2 to give the product **4** (70 mg, 73% yield): UV–vis (CH_2Cl_2) $\lambda = 244, 268, 348, 444$ nm; FT-IR 1780, 1744, 1500, 1072, 684 cm^{-1}; ^1H NMR δ 7.88 (d, $J = 8.7$ Hz, 4H), 7.28 (d, $J = 8.2$ Hz, 4H), 3.95–3.55 (m, 16H), 2.87 (s, 8H), 1.37 (t, $J = 7.0$ Hz, 24H); ^{13}C NMR δ 239.47, 169.27, 164.24, 130.99, 124.55, 118.70, 43.70, 25.53, 12.63.

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CONHCH(CH_3)_2$ (5a). Isopropylamine (50 μL, 1 mmol) was added to a solution of **2** (105 mg, 0.1 mmol) in DMF (4 mL) and stirred at 25 °C for 10 min. Water (36 mL) was added while stirring vigorously to precipitate the complex. The product was filtered, washed with water and hexanes, and then recrystallized from dichloromethane by adding hexanes to give the green solid **5a** (70 mg, 70% yield): UV–vis (CH_2Cl_2) $\lambda = 234, 264, 346$ nm ($\epsilon = 13000$); FT-IR 1639, 1525, 1435, 1093, 745, 694, 521 cm^{-1}; ^1H NMR δ 7.85–7.70 (m, 12H), 7.38–7.15 (m, 20H), 6.88 (d, $J = 8.4$ Hz, 2H), 5.76 (m, 1H), 4.23 (m, 1H), 1.26 (d, $J = 6.4$ Hz, 6H); ^{13}C NMR δ 163.62, 158.19, 135.33, 133.29, 132.17, 131.67, 130.70, 128.22, 121.76, 42.81, 23.13; $^{31}P\{^1H\}$ NMR δ −21.05 (s). Anal. Calcd for $C_{46}H_{42}Cl_3N_2OP_2Re{\cdot}0.5CH_2Cl_2$: C, 53.86; H, 4.15; N, 2.70. Found: C, 53.89; H, 4.09; N, 2.77.

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CONHCH(CH_3)CH(CH_3)_2$ (5b). The procedure described for the synthesis of **5a** was repeated using **2** (105 mg, 0.10 mmol) and 2-amino-3-methylbutane (87 mg, 1.00 mmol) to give the green solid **5b** (70 mg, 69% yield): UV–vis (CH_2Cl_2) $\lambda = 234, 264, 346$ nm ($\epsilon = 11\,437$); FT-IR 1655, 1536, 1435, 1093, 745, 694, 521 cm^{-1}; ^1H NMR δ 7.88–7.68 (m, 12H), 7.40–7.10 (m, 20H), 6.88 (d, $J = 7.4$ Hz, 2H), 5.75 (m, 1H), 4.02 (m, 1H), 1.80 (m, 1H), 1.17 (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.0$ Hz, 6H); ^{13}C NMR δ 165.22, 157.61, 134.73, 131.51, 131.09, 130.09, 127.59, 127.11, 121.20, 50.71, 32.86, 18.51, 17.36; $^{31}P\{^1H\}$ NMR δ −19.46.

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CONH(CH_2)_2Ph$ (5c). The procedure described for the synthesis of **5a** was repeated using **2** (50 mg, 0.05 mmol) and phenethylamine (50 μL, 0.50 mmol) to give the green complex **5c** (35 mg, 67%): UV–vis (CH_2Cl_2) $\lambda = 232, 264, 344$ nm ($\epsilon = 10\,598$); FT-IR 1665, 1541, 1093, 747, 694, 521 cm^{-1}; ^1H NMR δ 7.90–7.70 (m, 12H), 7.45–7.15 (m, 23H), 7.08 (d, $J = 8.4$ Hz, 2H), 6.82 (d, $J = 8.4$ Hz, 2H), 5.96 (m, 1H), 3.67 (q, $J = 6.7$ Hz, 2H), 2.92 (t, $J = 6.7$ Hz, 2H); ^{13}C NMR δ 166.48, 158.10, 139.12, 135.30, 132.08, 131.69, 131.15, 130.65, 129.23, 128.21, 127.87, 127.19, 121.77, 41.75, 35.87; $^{31}P\{^1H\}$ NMR δ −19.83 (s).

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CONHCH_2Ph$ (5d). The procedure described for the synthesis of **5a** was repeated using **2** (105 mg, 0.1 mmol) and benzylamine (110 μL, 1 mmol), and the crude product was recrystallized by slow diffusion of ethanol into a dichloromethane solution to give the green complex **5d** (75 mg, 72% yield): UV–vis (CH_2Cl_2) $\lambda = 234, 264, 344$ nm ($\epsilon = 13\,398$); FT-IR 1656, 1093, 745, 694, 521 cm^{-1}; ^1H NMR δ 7.82–7.73 (m, 12H), 7.40–7.30 (m, 5H), 7.26–7.17 (m, 20H), 6.86 (d, $J = 8.4$ Hz, 2H), 6.35 (t, $J = 5.2$ Hz, 1H), 4.58 (d, $J = 5.2$ Hz, 2H); ^{13}C NMR δ 166.30, 158.27, 138.19, 135.20, 133.97, 132.66, 132.06, 131.64, 130.63, 129.31, 128.56, 120.17, 121.75, 44.71; $^{31}P\{^1H\}$ NMR δ −21.29 (s). Anal. Calcd for $C_{50}H_{42}Cl_3N_2O_2P_2Re{\cdot}0.25CH_2Cl_2$: C, 56.74; H, 3.98. Found: C, 56.92; H, 3.60.

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CON(CH_2)_4$ (5e). The procedure described for the synthesis of **5a** was repeated using **2** (50 mg, 0.05 mmol) and pyrrolidine (50 μL, 0.50 mmol), and the crude product was recrystallized by slow diffusion of ethanol into a dichloromethane solution to give the green complex **5e** (35 mg, 70% yield) and recrystallized from dichloromethane and ethanol: UV–vis (CH_2Cl_2) $\lambda = 232, 264, 344$ nm ($\epsilon = 10\,486$); FT-IR 1628, 1092, 745, 694, 521 cm^{-1}; ^1H NMR δ 7.85–7.65 (m, 12H), 7.30–7.15 (m, 18H), 6.93 (d, $J =$

(19) Johnson, N. P.; Lock, C. J. L.; Wilkinson, G. *Inorg. Synth.* **1967**, *9*, 145–148.

8.0 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H), 3.58 (t, J = 6.4 Hz, 2H), 3.22 (t, J = 6.4 Hz, 2H), 2.05−1.82 (m, 4H); ^{13}C NMR δ 168.65, 156.85, 135.31, 132.16, 131.66, 131.20, 130.60, 128.14, 121.64, 49.82, 46.73, 26.81, 24.79; ^{31}P{^{1}H} NMR δ −21.00 (s). Anal. Calcd for $C_{47}H_{42}Cl_3N_2OP_2Re\cdot0.5CH_2Cl_2$: C, 54.39; H, 4.10; N, 2.67. Found: C, 54.55; H, 4.13; N, 2.66.

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CON(CH_2CH_2)_2O$ (5f). The procedure described for the synthesis of **5a** was repeated using **2** (105 mg, 0.10 mmol) and morpholine (88 μL, 1.00 mmol), and the precipitated product was recrystallized by slow diffusion of ethanol into a dichloromethane solution to give the green complex **5f** (80 mg, 78%): UV−vis (CH_2Cl_2) λ = 234, 264, 344 nm (ϵ = 13 922); FT-IR 1636, 1093, 746, 694, 521 cm^{-1}; ^{1}H NMR δ 7.85−7.65 (m, 12H), 7.30−7.15 (m, 18H), 6.88 (d, J = 8.0 Hz, 2H), 6.81 (d, J = 8.0 Hz, 2H), 3.99 (m, 2H), 3.80−3.50 (m, 4H), 3.25 (m, 2H); ^{13}C NMR δ 169.39, 156.93, 135.33, 132.22, 131.73, 131.17, 130.62, 128.16, 121.85, 61.12, 48.64; ^{31}P{^{1}H} NMR δ −21.36 (s). Anal. Calcd for $C_{47}H_{42}Cl_3N_2O_2P_2Re\cdot0.5CH_2Cl_2$: C, 53.57; H, 4.04; N, 2.63. Found: C, 53.16; H, 3.92; N, 2.64.

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CONHCH(CH_3)CO_2Et$ (5g). Triethylamine (300 μL, 2.00 mmol) was added to a solution of alanine ethyl ester hydrochloride (303 mg, 2.00 mmol) in DMF (4 mL), and the solution was stirred for 15 min. A solution of complex **2** (210 mg, 0.20 mmol) in DMF (4 mL) was then added, and the mixture was stirred for 10 min. Water (72 mL) was added, and the precipitated product **5g** was isolated by filtration and was subsequently recrystallized by addition of hexanes to a CH_2Cl_2 solution (140 mg, 67% yield): UV−vis (CH_2Cl_2) λ = 232, 264, 342 nm (ϵ = 12 000); FT-IR 1737, 1666, 1092, 750, 693, 521 cm^{-1}; ^{1}H NMR δ 7.85−7.68 (m, 12H), 7.35−7.15 (m, 20H), 6.87 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 7.2 Hz, 1H), 4.70 (m, 1H), 4.25 (q, J = 7.0 Hz, 2H), 1.51 (d, J = 6.8 Hz, 3H), 1.32 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 172.90, 165.28, 157.90, 134.70, 131.54, 131.11, 130.70, 130.09, 127.59, 121.19, 61.77, 48.63, 18.38, 14.01; ^{31}P{^{1}H} NMR δ -21.50 (s). Anal. Calcd for $C_{48}H_{44}Cl_3N_2OP_2Re$: C, 54.83; H, 4.22; N, 2.66. Found: C, 54.83; H, 4.18; N, 2.79.

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CONHCH(CH_2SH)CO_2Et$ (5h). The procedure described for the synthesis of **5g** was repeated using the cysteine ethyl ester hydrochloride (370 mg, 2.00 mmol), DMF (3 mL), triethylamine (300 μL, 2.00 mmol), **2** (210 mg, 0.20 mmol), DMF (3 mL), and water (54 mL). The product was recrystallized from dichloromethane and hexanes to give the green complex **5h** (160 mg, 74% yield): UV−vis (CH_2Cl_2) λ = 234, 264, 336 nm (ϵ = 14 870); FT-IR 1737, 1665, 1093, 746, 694, 521 cm^{-1}; ^{1}H NMR δ 7.82−7.70 (m, 12H), 7.35−7.15 (m, 20H), 6.88 (d, J = 8.0 Hz, 2H), 4.99 (m, 1H), 4.35−4.25 (m, 3H), 3.20−3.05 (m, 2H), 1.34 (t, J = 7.6 Hz, 3H); ^{31}P{^{1}H} NMR δ −21.23 (s).

Synthesis of $Cl_3(Ph_3P)_2Re{=}N\text{-}C_6H_4CONH(CH_2)_2NH$−Biotin (5i). The procedure described for the synthesis of **5g** was repeated with **6** (108 mg, 0.38 mmol), DMF (6 mL), triethylamine (86 μL, 0.57 mmol), complex **2** (200 mg, 0.19 mmol), DMF (6 mL), and water (108 mL). The product was recrystallized from dichloromethane and hexanes to give the green complex **5i** (107 mg, 49%): UV−vis (CH_2Cl_2) λ = 232, 264, 342 nm (ϵ = 7045); FT-IR 1705, 1655, 1544, 1435, 1093, 747, 694, 521 cm^{-1}; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 7.88−7.68 (m, 12H), 7.48−7.22 (m, 20H), 6.88 (d, J = 8.0 Hz, 2H), 4.55−4.40 (m, 1H), 4.35−4.22 (m, 1H), 3.58−3.32 (m, 4H), 3.20−2.65 (m, 3H), 2.23 (t, J = 8 Hz, 2H), 1.85−1.25 (m, 4H); ^{13}C NMR ($CDCl_3$+CD_3OD) δ 175.71, 167.42, 157.95, 135.06, 133.79, 131.87, 131.42, 130.57, 128.66, 128.07, 121.67, 62.25, 60.50, 55.73, 40.99, 40.58, 39.21, 35.87, 28.33, 25.66; ^{31}P{^{1}H} NMR δ −20.85 (s).

X-ray Structure Determination of $Cl_3(PPh_3)_2Re{=}N\text{-}C_6H_4CO_2N(COCH_2)_2\cdot(CH_2Cl_2)_{1.43}(EtOH)_{0.57}$. Complex **2** was crystallized by slow diffusion of ethanol into a CH_2Cl_2 solution of **2** at room temperature to give green, rod-shaped crystals of the complex $\mathbf{2}\cdot(CH_2Cl_2)_{1.43}\cdot(EtOH)_{0.57}$. A suitable crystal was suspended in viscous mineral oil, mounted on a glass fiber, and cooled to −70 °C. Data collection was performed by a Siemens R3m/V diffractometer operating in the θ−2θ scan mode with graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å) as previously described.[20] Intensities were corrected for Lorentz and polarization effects, and empirical absorption corrections were applied based on a set of ψ scans. The structure was solved by direct methods using Siemens' SHEXTL PLUS structure package. The unit cell and lack of systematic absences indicated a Laue symmetry of triclinic and the space group $P\bar{1}$. Two solvent molecules are included in the asymmetric unit, with one exhibiting complex disorder. This site refined adequately for 57% occupancy by EtOH and 43% occupancy by CH_2Cl_2, disordered over three positions. The structure was refined with full-matrix least-squares, and all non-hydrogen atoms in **2** and the ordered CH_2Cl_2 were refined anisotropically. The positions of the hydrogen atoms were calculated (C−H = 0.95 Å) and allowed to ride isotropically on their respective carbons atoms during refinement. Refinement of the data converged with a goodness-of-fit of 1.20 and final residuals (for 7463 data with $F > 4\sigma_F$) of R = 3.44% and R_w = 4.19%. Crystallographic data are presented in Table 1; selected bond distances and angles are given in Table 2.

Acknowledgment. J.B.A. thanks the USAMRC Breast Cancer Research Program DAMD17-97-1-7120 and ACS-PRF for financial support. M.V.V. and M.S.H. were supported by NIH-MBRS undergraduate fellowships.

Supporting Information Available: Complete tabulations of crystallographic data, bond lengths and angles, atomic coordinates, and thermal parameters, a completely labeled ball-and-stick diagram, and copies of ^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H} NMR spectra for complexes **4**, **5b**, **5c**, **5h**, and **5i**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM990929W

(20) Bryan, J. C.; Burrell, A. K.; Miller, M. M.; Smith, W. H.; Burns, C. J.; Sattelberger, A. P. *Polyhedron* **1993**, *12*, 1769−1777.

The authors thank the National Science Foundation of China for financial support of this work.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1252). Services for accessing these data are described at the back of the journal.

References

Bharadwaj, P. K., Schugar, H. J. & Potenza, J. A. (1991). *Acta Cryst.* C**47**, 754–757.

Laity, H. L. & Taylor, M. R. (1995). *Acta Cryst.* C**51**, 1791–1793.

Lundberg, B. K. S. (1966). *Acta Cryst.* **21**, 901–909.

Parvez, M. & Rusiewicz, M. (1995). *Acta Cryst.* C**51**, 2277–2279.

Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.

Sheldrick, G. M. (1993). *SHELXL93. Program for the Refinement of Crystal Structures.* University of Göttingen, Germany.

Sheldrick, G. M. (1994). *SHELXTL/PC.* Version 5.0. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Sheldrick, G. M. (1996). *SADABS. Program for Empirical Absorption Correction of Area Detector Data.* University of Göttingen, Germany.

Siemens (1995). *SMART* and *SAINT. Area Detector Control and Integration Software.* Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Acta Cryst. (1998). C**54**, 1607–1608

Trichlorooxo(triphenylphosphine)(triphenylphosphine oxide)rhenium(V)

JEFFREY C. BRYAN,[a] MARC C. PERRY[b] AND JEFFREY B. ARTERBURN[b]

[a]*Chemical and Analytical Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831-6119, USA, and* [b]*Department of Chemistry, New Mexico State University, Box 30001, Department 3C, Las Cruces, NM 88003, USA. E-mail: bryanjc@ornl.gov*

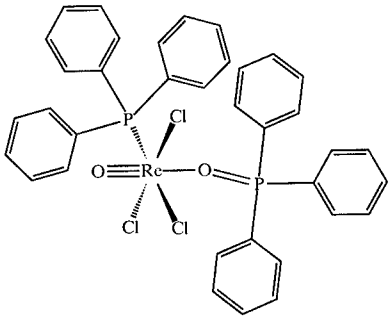
(Received 17 April 1998; accepted 10 June 1998)

Abstract

The title complex, $[ReCl_3O(C_{18}H_{15}OP)(C_{18}H_{15}P)]$, is produced in a reaction between $[Re(O)Cl_3(PPh_3)_2]$ and ethyl 2-hydroxymethyl sulfoxide. The structure is compared to that of $[Re(O)Cl_3(PPhEt_2)(OPPhEt_2)]$. The Re—Cl distances are shorter [2.361 (2)–2.384 (2) Å] and the Re—P distance is longer [2.506 (2) Å] in the title complex.

Comment

A variety of interesting and synthetically useful O-atom transfer reactions from sulfoxide substrates catalyzed by the precursor complex $[Re(O)Cl_3(PPh_3)_2]$ have recently been reported (Bryan *et al.*, 1987; Arterburn & Perry, 1996; Arterburn & Nelson, 1996; Arterburn *et al.*, 1997). This compound was known to react with dimethyl sulfoxide in the presence of hydrochloric acid to form the mixed dimethylsulfide–triphenylphosphine oxide complex $[Re(O)Cl_3(SMe_2)(OPPh_3)]$. However, no intermediate complexes from the catalytic reactions in organic solvents have yet been structurally identified. The precursor complex was found to react with one equivalent of ethyl 2-hydroxyethyl sulfoxide, $CH_3CH_2S(O)CH_2CH_2OH$, at ambient temperature to give a purple solution. The title complex, (I), and amorphous purple solids were obtained following precipitation with diethyl ether. These results are consistent with catalytic pathways involving coordinated Re^V–oxo complexes as intermediates.



(I)

A distorted octahedral coordination geometry is observed around Re (Fig. 1). The major distortion is an increase in the O1—Re—Cl angles, which is commonly observed in octahedral complexes containing a

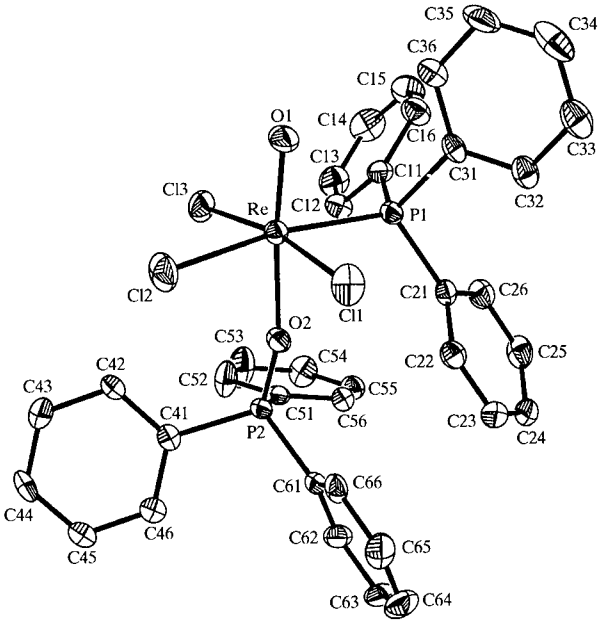


Fig. 1. The molecular structure of (I) showing 50% probability displacement ellipsoids. H atoms have been omitted for clarity.

multiply bonding ligand (Nugent & Mayer, 1988; Bryan *et al.*, 1987). The location of softer ligands *cis* to the oxo ligand is also often observed (Bryan *et al.*, 1987). The short Re–oxo (O1) bond length of 1.669 (4) Å is consistent with a strong multiple bond (Nugent & Mayer, 1988). The structure of (I) is very similar to the closely related $[Re(O)Cl_3(PPhEt_2)(OPPhEt_2)]$ (Sergienko, 1994; Sergienko *et al.*, 1982). The Re—Cl distances are shorter [2.361 (2)–2.384 (2) Å] in (I) than in $[Re(O)Cl_3(PPhEt_2)(OPPhEt_2)]$ [2.394 (4)–2.407 (4) Å], while the Re—P distance is longer [2.506 (2) *versus* 2.464 (4) Å]. These differences can be understood by the fact that PPh_3 is a weaker donor ligand than $PPhEt_2$.

Experimental

The preparation of (I) has been previously reported (Grove & Wilkinson, 1966; Bryan *et al.*, 1987). Green crystals suitable for X-ray diffraction were prepared by slow diffusion of methyl *tert*-butyl ether into an acetone solution of the complex.

Crystal data

$[ReCl_3O(C_{18}H_{15}OP)(C_{18}H_{15}P)]$
M_r = 849.14
Monoclinic
$P2_1/c$
a = 18.797 (2) Å
b = 9.5553 (6) Å
c = 19.4819 (13) Å
β = 109.574 (6)°
V = 3296.9 (5) Å^3
Z = 4
D_x = 1.711 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 10.4–13.0°
μ = 4.06 mm^{-1}
T = 173 K
Prism
0.46 × 0.27 × 0.23 mm
Green

Data collection

Nonius CAD-4 diffractometer
ω scans
Absorption correction: ψ scan (Siemens, 1997)
T_{min} = 0.274, T_{max} = 0.393
8509 measured reflections
7561 independent reflections
5690 reflections with $I > 2\sigma(I)$

R_{int} = 0.039
θ_{max} = 27.5°
$h = 0 \rightarrow 24$
$k = -12 \rightarrow 5$
$l = -25 \rightarrow 23$
3 standard reflections
frequency: 120 min
intensity decay: 3%

Refinement

Refinement on F^2
$R(F)$ = 0.040
$wR(F^2)$ = 0.099
S = 1.074
7561 reflections
397 parameters
H atoms not refined
$w = 1/[\sigma^2(F_o^2) + (0.0502P)^2 + 4.6318P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max}$ = −0.001
$\Delta\rho_{max}$ = 2.40 e Å^{-3}
$\Delta\rho_{min}$ = −1.47 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

Re—Cl1	2.373 (2)	Re—O1	1.669 (4)
Re—Cl2	2.361 (2)	Re—O2	2.082 (4)
Re—Cl3	2.384 (2)	P2—O2	1.508 (4)
Re—P1	2.506 (2)		
Cl1—Re—Cl2	86.53 (6)	Cl2—Re—O2	87.33 (11)
Cl1—Re—Cl3	169.74 (6)	Cl3—Re—P1	95.09 (5)
Cl1—Re—P1	89.69 (5)	Cl3—Re—O1	94.07 (19)
Cl1—Re—O1	95.25 (19)	Cl3—Re—O2	84.17 (12)
Cl1—Re—O2	87.23 (12)	P1—Re—O1	86.82 (16)
Cl2—Re—Cl3	87.50 (6)	P1—Re—O2	84.90 (11)
Cl2—Re—P1	171.52 (6)	O1—Re—O2	171.35 (18)
Cl2—Re—O1	101.07 (16)	Re—O2—P2	165.1 (3)

Anisotropic displacement parameters were used for all non-H atoms. All H atoms were placed in calculated positions (C—H = 0.95 Å), refined using a riding model, and given isotropic displacement parameters equal to 1.2 times the equivalent isotropic displacement parameter of the atom to which they are attached. The highest eight peaks in the final difference map (electron density greater than 0.8 e Å^{-3}) are located approximately 1 Å from Re.

Data collection: *CAD-4-PC* (Enraf–Nonius, 1993). Cell refinement: *CAD-4-PC*. Data reduction: *XCAD4* (Harms, 1995). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *SHELXTL* (Siemens, 1997). Software used to prepare material for publication: *PLATON* (Spek, 1998).

This work was supported by the US Army Medical Research Acquisition Activity.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1142). Services for accessing these data are described at the back of the journal.

References

Arterburn, J. B. & Nelson, S. L. (1996). *J. Org. Chem.* **61**, 2260–2261.
Arterburn, J. B. & Perry, M. C. (1996). *Tetrahedron Lett.* **37**, 7941–7944.
Arterburn, J. B., Perry, M. C., Nelson, S. L., Holguin, M. S. & Dible, B. R. (1997). *J. Am. Chem Soc.* **119**, 9309–9310.
Bryan, J. C., Stenkamp, R. E., Tulip, T. H. & Mayer, J. M. (1987). *Inorg. Chem.* **26**, 2283–2288.
Enraf–Nonius (1993). *CAD-4-PC*. Version 1.2. Enraf–Nonius, Delft, The Netherlands.
Grove, D. E. & Wilkinson, G. (1966). *J. Chem. Soc. A*, pp. 1224–1230.
Harms, K. (1995). *XCAD4. Program for the Lp Correction of Enraf–Nonius Four-Circle Diffractometer Data*. University of Marburg, Germany.
Nugent, W. A. & Mayer, J. M. (1988). In *Metal-Ligand Multiple Bonds*. New York: Wiley.
Sergienko, V. S. (1994). *Zh. Neorg. Khim.* **39**, 1641–1645.
Sergienko, V. S., Porai-Koshits, M. A., Mistryukov, V. E. & Kotegov, K. V. (1982). *Koord. Khim.* **8**, 230–235.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1993). *SHELXL93. Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.
Siemens (1997). *SHELXTL*. Version 5.04/IRIX. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Spek, A. L. (1998). *PLATON. A Multi-Purpose Crystallographic Tool*. University of Utrecht, The Netherlands.